Postgraduate Medicine

Volume 27 · Number 3

MARCH · 1960

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

TABLE *of* CONTENTS

Special Issue

Evaluation of Early Diagnosis of Cancer

Annual Scientific Session, American Cancer Society

Introduction
HAROLD S. DIEHL, M.D. 268

Scientific Session of the American Cancer Society; Purpose of the Symposium
EUGENE P. PENDERGRASS, M.D. 269

What Is Early Cancer?
DANELY P. SLAUGHTER, M.D. 271

What Is an Adequate "Cancer Checkup?"
EMERSON DAY, M.D. 274

The Changing Responsibility of the Practicing Physician in Cancer Detection
I. PHILLIPS FROHMAN, M.D. 285

Value of Periodic Examinations in Detecting Cancer of the Rectum and Colon
RALPH E. L. HERTZ, M.D., MICHAEL R. DEDDISH, M.D. AND EMERSON DAY, M.D. 290

Value of Periodic Examination in Head and Neck Cancer
GRANTLEY WALDER TAYLOR, M.D. 295

Value of Periodic Examination in Early Cancer of the Breast
EDWARD F. LEWISON, M.D. 297

Value of Periodic Examinations in Detecting Cancer of the Genitourinary System
ROGER BAKER, M.D. 301

(Continued on page A-4)

Postgraduate Medicine is published monthly at Minneapolis, Minn., by IPMA Publishing Co., G. Victor Lowrie, executive vice-president; William H. Hull, professional relations manager; Muriel D. Ries, circulation manager; Fred Couzens, Eastern manager, 420 Lexington Ave., New York 17, N.Y., telephone Murray Hill 4-7752; Arthur G. Sullivan, Jr., Central-West manager, 203 North Cedar Street, Horicon, Wis., telephone Hunter 5-2003. Advertising representatives: McDonald-Thompson, 1008 Western Ave., Seattle 1, Wash.; 625 Market St., San Francisco 5, Calif.; 3727 W. 6th St., Los Angeles 5, Calif.; 2727 Oak Lane Ave., Dallas 19, Tex.; 3217 Montrose Blvd., Houston 6, Tex.; 620 Sherman St., Denver 3, Colo. Publication date: 10th of the month. Subscription rate $10.00 a year in the United States and Canada; $12.00 in foreign countries. Two volumes a year. Address all editorial and business correspondence to **Postgraduate Medicine**, Essex Building, Minneapolis 3, Minn., telephone Federal 9-8836. © 1960 by IPMA Publishing Co. Title Reg. U. S. Pat. Off. Entered as second-class matter February 27, 1947, at the post office at Minneapolis, Minn., under the act of March 3, 1879. Additional entry at Long Prairie, Minn., under date of April 14, 1948. Printed in U.S.A.

Early Diagnosis of Cancer of the Gastrointestinal Tract
DONALD B. SHAHON, M.D. AND OWEN H. WANGENSTEEN, M.D. 306

Value of Periodic Examinations in Detecting Early Lung Cancer
ROBERT B. BROWN, M.D. 312

The Problem of the Precancerous Lesion
FRED W. STEWART, M.D. 317

Lay Education in Cancer
E. CUYLER HAMMOND, D.SC. 324

Precancerous Lesions of the Breast; How to Treat Them
MURRAY M. COPELAND, M.D. 332

Recognition and Management of the Cutaneous Precanceroses
FRANCIS W. LYNCH, M.D. 337

Leukoplakia of the Intraoral Cavity
WILLIAM S. MAC COMB, M.D. 349

Precancerous Lesions of the Uterus; How to Treat Them
JOHN B. GRAHAM, M.D. 356

Precancerous Lesions of the Stomach; How to Treat Them
RUSSELL S. BOLES, M.D. 359

Precancerous Lesions and Other Conditions of the Thyroid Gland
THOMAS J. ANGLEM, M.D. 366

The Pigmented Mole
GEORGE T. PACK, M.D. AND JEFF DAVIS, M.D. 370

Clinical Staging and Proper End-results Reporting of Cancer
R. LEE CLARK, JR., M.D. 383

Treatment of Early Cancer of the Breast
JEROME A. URBAN, M.D. 389

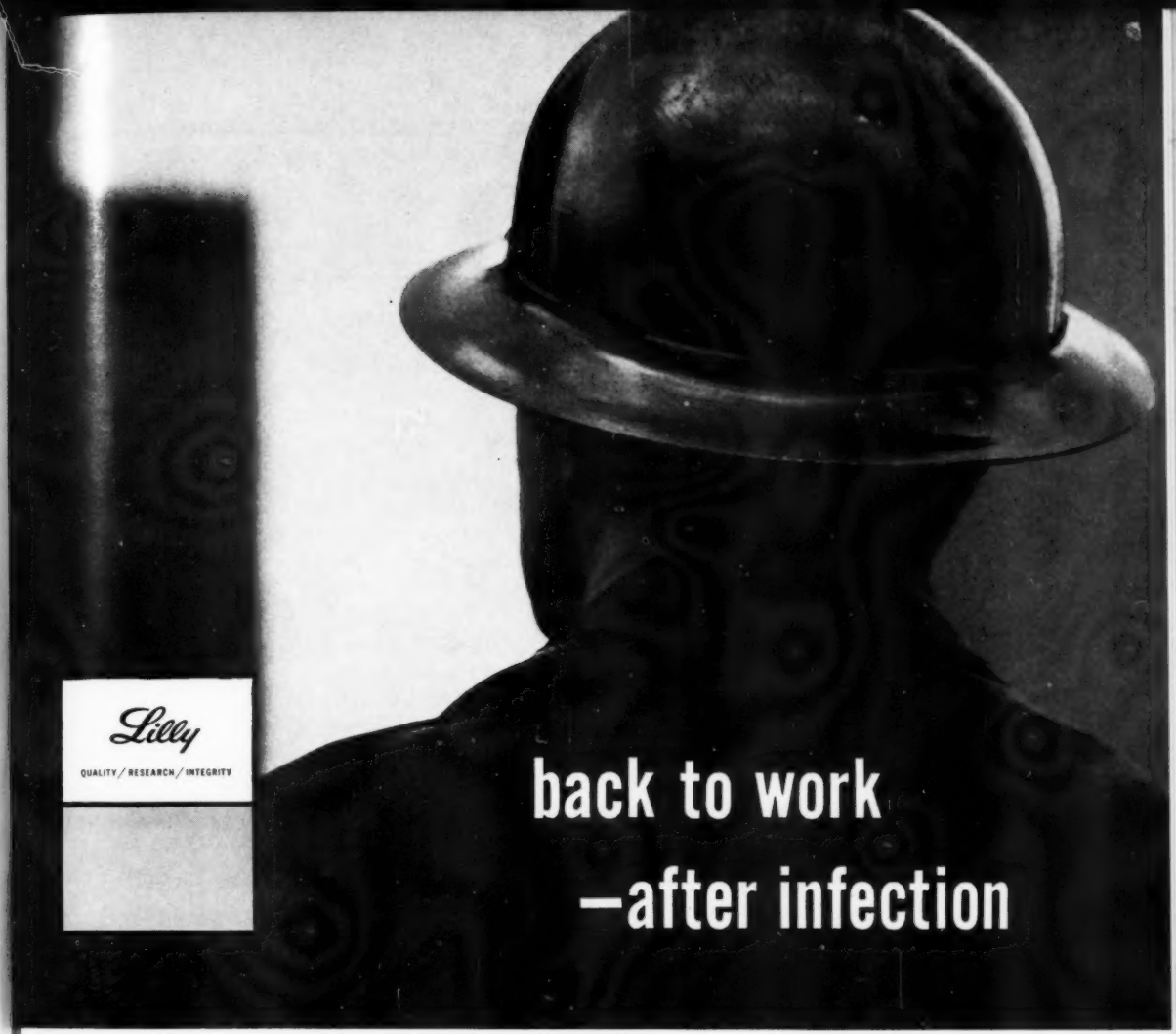
Early Cancer of the Larynx
EDGAR L. FRAZELL, M.D. AND FRANK R. GEROLD, M.D. 394

Treatment of Early Cancer of the Cervix
HOWARD ULFELDER, M.D. 398

Early Cancer of the Rectum
NEIL W. SWINTON, M.D. AND JOSEPH C. SNOW, M.D. 401

Surgical Treatment of Early Carcinoma of the Face
KENNETH L. PICKRELL, M.D., NICHOLAS GEORGIADE, M.D.,
JEROME ADAMSON, M.D. AND GUIDO MATTON, M.D. 406

(Continued on page A-6)



V-CILLIN K® produces high levels of antibacterial activity

Infections resolve rapidly with V-Cillin K. All patients absorb this oral penicillin and show therapeutic blood levels with recommended doses. The high levels of antibacterial activity achieved by V-Cillin K offer greater assurance of bactericidal concentration in the tissues—a more dependable response.

Dosage: 125 or 250 mg. three times daily. Supplied as scored tablets of 125 and 250 mg.

also available

V-Cillin K, Pediatric: A taste treat for young patients. In bottles of 40 and 80 cc. Each 5-cc. teaspoonful provides 125 mg. of V-Cillin K.

V-Cillin K® (penicillin V potassium, Lilly)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

053222

Early Treatment of Cancer of the Thyroid Gland
JOHN C. McCLINTOCK, M.D. 416

Early Cancer of the Oral Cavity With Special Reference to Cancer of the Tongue
ARNOLD J. KREMEN, M.D. AND STUART W. ARHELGER, M.D. 422

DEPARTMENTS

MEETINGS AND POSTGRADUATE COURSES 270

YOUR QUESTIONS ANSWERED A-18
Determination of Death
Gold Salts Dosage

WHAT'S HAPPENING IN MEDICINE ..... Facing A-32-33

LABORATORY NOTES A-34
New Interest in Urine Sugars Other Than Glucose
ELLIS S. BENSON, M.D.

FORENSIC MEDICINE—BOOK REVIEWS A-58
The Law of Medical Practice
Reviewed by JACK L. SACHS, LL.B.
The Physician and the Law
Reviewed by EDWIN J. HOLMAN, LL.B.

RADIOLOGY FOR PRACTICING PHYSICIANS A-87
Roentgen Diagnosis of Lesions of the Esophagus, Part 1
JAMES R. WILLIAMS, M.D. AND PAUL C. HODGES, M.D.

MEDICINE FROM ABROAD A-98

NEW FOR YOUR ARMAMENTARIUM A-130

FINANCIAL PLANNING FOR THE MEDICAL PRACTITIONER
J. K. Lasser Institute ..... Facing A-158-159

THE MEDICAL BOOKMAN A-160

PRODUCTS BY THERAPY INDICATIONS A-182

DR. PEPYS' PAGES. Morris Fishbein, M.D. A-194

THE MEDICAL MUSE. Richard Armour A-198

INDEX TO TECHNICAL EXHIBITS A-203

SOMA RELIEVES PAIN in a unique way by modifying central perception of pain without abolishing natural defense reflexes.

SOMA RELAXES MUSCLE SPASM . . . approximately 8 times more potent than meprobamate or mephenesin.

PHYSICIANS' REPORTS:

"Marked pain-relieving effects of the new drug [SOMA] were seen in conditions involving muscle spasm and stiffness, whether acute or chronic. Relief from pain was usually rapid and sometimes dramatic." (90 patients.)
Kuge, T.: Submitted for publication.

"In 86 percent of the patients there were excellent or good results. . . . Relief of pain was noted by the patients' statements, by the diminished need for analgesic drugs, and by improved sleep." (154 patients.)
Wein, A. B.: The Use of Carisoprodol in Orthopedic Surgery and Rehabilitation. Proceedings of the Symposium on The Pharmacology and Clinical Usefulness of Carisoprodol. Wayne State University Press, Detroit, 1959, p. 156.

In a double-blind study, SOMA was reported to be "clinically effective to a highly significant degree." (92 patients.)
Cooper, C. D., and Epstein, J. H.: The Clinical Evaluation of Carisoprodol by a double-blind technique. Ibid. p. 97.

Notable safety—extremely low toxicity; no known contraindications; side effects are rare; drowsiness may occur, usually at higher dosage

Rapid action—starts to act quickly

Sustained effect—relief lasts up to 6 hours

Easy to use—usual adult dose is one 350 mg. tablet 3 times daily and at bedtime

Supplied—as white, coated, 350 mg. tablets, bottles of 50.
Also available for pediatric use: 250 mg. orange capsules, bottles of 50.

SOMA T.M.
(carisoprodol Wallace)

BIBLIOGRAPHY: 1. Berger, F.M., Kletzkin, M., Ludwig, B.J., Margolin, S. and Powell, L. S.: J. Pharm. Exp. Ther. *127*:66 (Sept.) 1959. 2. Leake, Chauncey D.: Proceedings of the Symposium on The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959, p. 8. 3. Kestler, Otto: Ibid. p. 143. 4. Proctor, Richard C.: Ibid. p. 122. 5. Berger, Frank M., Ibid. p. 25. 6. Goodgold, Joseph, Hohmann, Thomas and Tajima, Toshihiro: Ibid. p. 66. 7. Gammon, George D. and Tucker, Samuel: Ibid. p. 70. 8. Baird, Henry W. and Menta, Dominic A.: Ibid. p. 85. 9. Cooper, C. David and Epstein, Jerome H.: Ibid. p. 97. 10. Korst, Donald R., Gerard, R. W., Miller, James G., Small, Iver F., Graham, I. J. and Winkelman, Eugene I : Ibid. p. 104. 11. Friedman, Arnold P.: Ibid. p. 115. 12. Trimpi, Howard D.: Ibid. p. 150. 13. Wein, Arthur B.: Ibid. p. 156. 14. Olds, James and Travis, R. P.: Ibid. p. 39. 15. Hess, Eckhard H., Polt, James M. and Goodwin, Elizabeth: Ibid. p. 51. 16. Phelps, Winthrop M.: Ibid. p. 131. 17. Spears, Catherine E.: Ibid. p. 138. 18. Hyde, L. P. and Hough, Charles E.: Ibid. p. 166. 19. Spears, Catherine E. and Phelps, Winthrop M.: Arch Pediat., *76*:287 (July) 1959. 20. Phelps, Winthrop M.: Arch. Pediat., *76*:243 (June) 1959. 21. Friedman, Arnold P.: Paper presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc., New York, Sept. 30, 1959. 22. Frankel, Kalman: Ibid. 23. Fransway, Robert L.: Ibid. 24. Kuge, T.: Unpublished reports.

Literature and samples on request WALLACE LABORATORIES, New Brunswick, New Jersey

Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• DETERMINATION OF DEATH

Q. A drowning occurred at a local beach. No one knows how long the body was under water before it was discovered. However, artificial respiration was begun immediately after discovery of the victim and was continued for about one hour. During this hour two separate physicians attended the victim and could detect no sign of life. After some discussion by the physicians with the lifeguards, the artificial respiration was stopped and the body was taken to the morgue.

Since then, there has been much criticism of the doctors' action in having stopped artificial respiration before rigor mortis had set in. Apparently the training given by the Royal Life Saving Society states that this latter is the proper procedure.

Also, a recent issue of *Health*, published by the Health League of Canada, contained an article on drowning which has caused concern among local physicians. This publication is supervised by medical specialists and usually contains reliable information written for the laity.

Would you discuss the latest theories on drowning. How could survival be possible if a body was without oxygen for more than 10 minutes? Is stethoscopic examination of the heart of any value in determining death in a case of drowning?

M.D.—Ontario

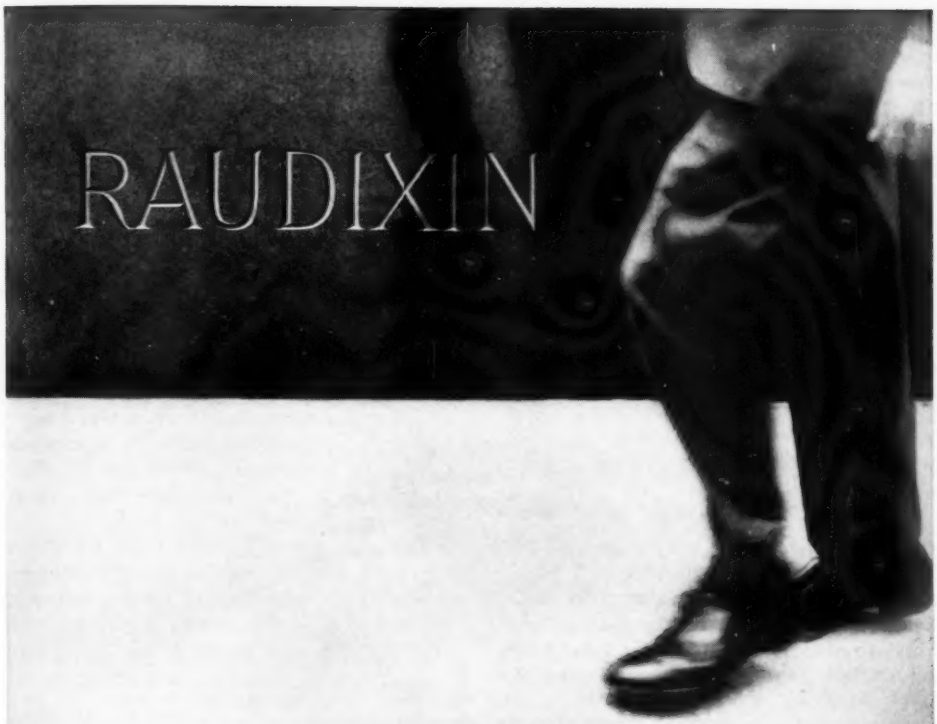
A. There is no exact, specific type of drowning. There is that drowning in which the larynx is open and water actually finds its way into the lungs. However, in a much higher percentage of cases, drowning is, in reality, a form of asphyxia secondary to laryngospasm, and there is very little water in the lungs. It also makes a definite difference in the pathologic findings whether the drowning occurred in fresh or salt water, and whether or not, at the time of relaxation of the larynx, the body was in an upright position or in such a position that water could or could not leak into the lungs.

It is unfortunate but true that we have no exact way of knowing when a patient is really dead. Even in our most modern hospitals with all of the scientific equipment, all that we can really say is that there are "no signs of life," and we continue to work until such time as our basic experience indicates that the state of so-called suspended animation has now finally become irreversible. Even in these instances, one could occasionally resuscitate a heart, but a feeling that the brain would not return to normal function is a key to irreversibility.

One would assume that two minutes of acute hypoxia of the brain would result in irreparable damage, but this may be only cellular and diffuse and functionally reversible. After approximately three to five minutes, more areas of the brain would be damaged, so that it is no longer a case of localized disease of the brain, but a major dysfunction of the brain. There comes a time when a sufficient amount of the brain, especially the medullary areas, is so damaged that it cannot be restituted. However, I know of no signs which would inform you of exactly when this occurs. For example, the younger the individual, the more apt he is to return to normality. If there had been no major struggle prior to drowning, the amount of oxygen in the lungs might sustain life without any deficit for as long a period as three minutes.

The interesting thing that many people forget is that good artificial respiration may circulate enough blood—even in a heart that shows no sign

(Continued on page A-20)



Raudixin–the cornerstone of antihypertensive therapy–helps relieve the pressures in your patients–helps relieve the pressures on your patients / 50 and 100 mg. tablets whole root rauwolfia for exceptional patient response

SQUIBB Squibb Quality—the Priceless Ingredient

Squibb Whole Root Rauwolfia Serpentina/'RAUDIXIN'® IS A SQUIBB TRADEMARK

of beating—to the degree that life may be maintained over long periods of time.

To wait for rigor mortis is to require the abandonment of scientific knowledge. However, there is a tremendous moral, ethical and scientific responsibility placed on the physician when he pronounces a patient dead. It is difficult and hazardous, and can only be done after a sufficient period of time has elapsed so that the individual physician believes the brain has sustained so much damage it cannot come back. I believe that the heart may come back after many hours of insult. The brain is the problem in this kind of case.

In the final analysis, death can only be diagnosed by a physician based on his individual experience in a specific incident or case.

I know that this does not answer the question, but it does not do so because of the lack of instrumentarium or the inability to pinpoint the exact time of death.

Second consultant: The major common denominator of a public tragedy such as a drowning frequently is the emotional reaction of the spectators. This often may be expressed as overt hostility directed toward the unsuccessful rescuers. Similarly, such emotion very often distorts memory and adds to the normal tendency to elaborate on the events of years ago while recounting them to prove a point. It would seem that societies which need public support to function might go to otherwise excessive lengths to retain favor. This could explain the attitude of maintaining resuscitative efforts for four hours or until rigor mortis develops.

From the physiologic point of view, victims of drowning might be divided into two groups. One group consists of those who take large quantities of water into the lungs, resulting in massive electrolyte imbalance. If salt water has been inhaled, treatment should include rapid electrolyte washout, such as is achieved with the artificial kidney. Inhalation of fresh water requires rapid and careful replacement of electrolytes. Obviously, the usual means of manual ventilatory or expired-air ventilatory resuscitation would not be effective in such cases, regardless of how well applied or how long continued.

The other group includes those persons who have had severe protective laryngeal and bronchiolar spasm as a result of foreign matter such as water in the upper airway. A minimal amount of water has entered the lungs and the possibility

(Continued on page A-22)

for MUMPS
MUMPS IMMUNE GLOBULIN
(Human)
The gamma globulin fraction of blood from adult donors hyperimmunized with mumps virus vaccine. For prevention and treatment of mumps in children and adults. Supplied in 1.5 cc (child's dose) and 4.5 cc (adult's dose) vials.

for WHOOPING COUGH
PERTUSSIS IMMUNE GLOBULIN
(Human)
The gamma globulin fraction of blood from adult donors hyperimmunized with phase I pertussis vaccine. For prevention and treatment of whooping cough. Supplied in 1.5 cc (one dose) vials.

4
HYLAND GAMMA GLOBULIN "SPECIFICS"
Hyland
HYLAND LABORATORIES
4501 Colorado Blvd.
Los Angeles 39, Calif.
160 Lockwood Ave.
Yonkers, N. Y.

for MEASLES
IMMUNE SERUM GLOBULIN
(Human)
The gamma globulin fraction of pooled normal plasma from healthy adult donors. For prevention or attenuation of measles and infectious hepatitis. For prevention of recurrent infections associated with gamma globulin deficiency. Supplied in 2 cc vials and 10 cc vials

for POLIOMYELITIS
POLIOMYELITIS IMMUNE GLOBULIN
(Human)
Immune Serum Globulin which has been further tested and conforms to U. S. Public Health Service requirement for poliomyelitis antibody content For passive protection against paralytic poliomyelitis in addition to uses of Immune Serum Globulin above. Supplied in 2 cc and 10 cc vials.

INDICATIONS: Bidrolar is the therapy of choice in individuals past 40 since it strikes at the most common cause of constipation, namely biliary deficiency.

It is highly effective in managing constipation of atonic, dietary and psychogenic type; safely used in pregnancy, anorectal surgery and cathartic habituation.

DOSAGE: 1 tablet 1 or 2 times daily for mild constipation. 2 tablets b.i.d. or t.i.d. for severe constipation (until bowel movements are normal). To be taken with a full glass of water.

FORMULA: Each tablet contains: Dioctyl Sodium Sulfosuccinate 40 mg., Ox Bile Extract 60 mg.

SUPPLIED: In bottles of 30 and 100.

Bidrolar provides an efficient stool softener that keeps feces soft for easy evacuation; and ox bile, a natural stimulant of peristaltic activity without adverse effects or irritation of the intestinal mucosa. Ox Bile has long been recognized as a natural laxative that is neither irritating nor habit forming. It is similar in composition to natural bile. It contains all the bile salts—and in conjugated form—the form which is most effective. Ox bile stimulates the liver to increase free flow of natural bile thus promoting natural hydration of the stool.

BIDROLAR

SAMPLES AND LITERATURE ON REQUEST

FORREST COMPANY · 93 CROSBY STREET, NEW YORK 12, N.Y.

of resuscitating such persons is more favorable. Breath-holding ability varies widely; it can be developed so that the breath may be held for a remarkable length of time. This extends the viability of the victim, since the body uses available oxygen as totally as possible before the effects of hypoxia are experienced.

In cold northern waters, hypothermia most certainly occurs while the victim is under water; quite probably it decreases the consumption of oxygen, thus extending the time in which resuscitation may be effective. Profound circulatory collapse with cardiac dilatation may occur with the heart still feebly beating, although no heartbeat can be heard with the stethoscope. This type of hypothermic, hypoxic patient can be resuscitated if ventilated and warmed, even though he has been under water for a considerable period. If actual cardiac arrest has occurred, however, the resuscitation efforts are of little value unless cardiac massage after thoracotomy is done; it is obvious that this almost never is logical under the conditions prevailing in a drowning.

Logical criteria for ceasing to use resuscitation are difficult to apply, but certainly it is hard to agree that one should continue blindly for four hours or until rigor mortis develops. If, after about 60 to 90 minutes of producing adequate ventilation, a progressive decline of body temperature is noted, with dilated and unresponsive pupils, no heart tones or evidence of circulation, and continued poor skin color, the decision to stop resuscitative efforts should be considered. Steady or rising body temperature, any questionable heart tones, etc., certainly suggest prolonging any efforts until such criteria are no longer present or recovery occurs.

• GOLD SALTS DOSAGE

Q. Dosage schedules of gold sodium thiomalate for treating rheumatoid arthritis often are given as 40 or 50 mg. each week to a total of 500 to 1000 mg. Does the milligram dosage refer to the solution of gold salts or to the actual gold content, which is 50 per cent of this?

M.D.—California

A. The dosage recommended refers to the gold salts. The actual gold content is 50 per cent of this. The weekly dosage usually given is 1 cc. of the preparation containing 50 mg. gold sodium thiomalate or 25 mg. actual gold.

What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

ENZYMES IN ORTHOPEDIC INFECTIONS

American Academy of Orthopaedic Surgeons:

- Treatment with human fibrinolysin produced rapid healing in 21 of 28 patients with complicated infected wounds following orthopedic procedures. Most of these wounds had shown resistance to healing despite intensive therapy of other types. The most dramatic results were achieved in four patients in whom a large metallic prosthesis had been used to replace the femoral head. Complete healing occurred despite the fact that in two cases the prosthesis was exposed in the infected wound.—Dr. Eugene E. Cliffton, Cornell University Medical College, New York.

- In many cases of apical lung carcinoma, the initial symptoms are thought to indicate an obscure condition in the shoulder or are even labeled a functional complaint in the presence of pathologic findings in the lung. The classic symptoms of lung carcinoma are often absent in apical involvement. X-ray examination of the apexes of the lungs should be made in cases of persistent shoulder pain of obscure etiology.—Dr. Paul E. Dee, Rockford, Ill.

- Consistent relief from arthritic pain with a concomitant improvement in joint mobility and general functional capacity has resulted from so-called extended sympathetic denervation in 52 middle-aged and elderly patients with advanced painful rheumatoid arthritis and osteoarthritis of the hip joints or knee joints, or both. Neuropathic disorganizations of the affected joints have not occurred in follow-ups of the last five years.—Dr. Robert Herfort, St. Agnes Hospital, White Plains, N. Y.

- A study of 90 birth presentations of infants with congenital dislocations of the hip showed that 25.6 per cent were breech deliveries. The normal incidence of breech presentations in 3800 births at Ohio State University Health Center in 1956 was 3.4 per cent.—Dr. William S. Smith, Ohio State University College of Medicine, Columbus.

GENETIC LINK IN CEREBRAL PALSY

American Academy for Cerebral Palsy:

- A genetic study of 100 children with cerebral palsy at the Moody State School of Cerebral Palsy, Galveston, showed that in 15 families two or more children were affected. A brother and sister had identical forms of cerebral palsy, as well as bilateral congenital cataracts. Abnormalities were found in the chromosome patterns of both. The incidence of spontaneous abortion among mothers in the study group was 30 per cent.—Dr. Johanna Blumel, University of Texas Medical Branch, Galveston.

Controlling viral encephalomyelitis

Symposium on Eastern Viral Encephalomyelitis, University of Pennsylvania:

- Despite the lack of knowledge of the epidemiology of Eastern viral encephalomyelitis, the most important control measure is early diagnosis. No more than 72 hours should be required. In these times, when we must be alert to the possible use of biologic warfare, we must be sure that the condition is not something more deadly, devastating and difficult to handle than Eastern viral encephalomyelitis.—Dr. Richard E. Shope, Rockefeller Institute, New York.
- The combination of factors that led to the outbreak of Eastern viral encephalomyelitis in New Jersey and other Eastern states last summer does not occur very frequently. It requires a relatively high population of susceptible or nonimmune bird hosts, a high population of the principal mosquito *Culiseta melanura* in the swamps, a largely nonimmune horse population, and a hot, wet climate.—Dr. Roy W. Chamberlain, Public Health Service Communicable Disease Center, Montgomery, Ala.

Cardiac asthma—a misnomer

American Academy of Allergy:

- The term "cardiac asthma" was first popularized in 1929 to designate patients with failure of the left ventricle causing episodes of asthmatic breathing and signifying a poor prognosis. A study of more than 100 patients with asthma and coexistent cardiovascular disease, some of whom had been treated for cardiac asthma, and of more than 100 patients with organic chronic heart disease who were examined for evidence of asthma leads to the conclusion that cardiac disease is not a basic cause of asthma, that cardiac asthma is rare, and that the term actually is a misnomer. Coexistence of asthma and cardiac disease is not uncommon. The latter may play a role in the increased dyspnea of the asthmatic patients. These facts are clinically important since asthmatic patients who are treated solely for coexistent cardiac disease and who are refractory to such treatment improve when additional treatment for allergy is given.—Drs. Louis Tuft and Leonard S. Girsh, Philadelphia.
- Adequate corticosteroid therapy for asthma in children is less likely to be associated with growth suppression when cortisone rather than prednisone is used. The linear growth rate was charted in 11 children receiving prednisone for six months or longer. Growth retardation was evident in all the patients when the average daily dosage per square meter of body surface exceeded 5 mg. In 12 patients given cortisone, no growth retardation was evident even though the average daily dosage was 19 to 25 mg. in two patients, 26 to 35 mg. in two, 36 to 45 mg. in four, and 46 to 57 mg. in four.—Drs. Thomas E. Van Metre, Jr. and William A. Niermann, Baltimore.

Immune mechanism in rheumatic disease

Conference on Connective Tissue, New York Academy of Medicine:

- Animal studies have suggested that the persistence of fibrin in rheumatoid nodules involves a defective autoimmune response which prevents the resorption of fibrin in rheumatoid arthritis. Homologous fibrin implants underwent quick lysis and were replaced by collagen. Heterologous fibrin remained unchanged for as long as eight weeks. The reaction bore a striking resemblance to the reaction around the fibrinoid in a rheumatoid nodule. The congregation of histiocytes, lymphocytes and plasma cells around the fibroblastic capsule indicated an immune reaction. A circulating antibody to the implant also was detected.—Dr. L. E. Glynn, Canadian Red Cross Memorial Hospital, Taplow, Maidenhead, England.

AN AMES CLINIQUICK®

CLINICAL BRIEFS FOR MODERN PRACTICE

WHY IS DIABETES IN INFANTS SO DIFFICULT TO DIAGNOSE?

Because of the infrequency of the disease in this age group, its sudden onset, the profusion of inconsistent presenting symptoms, and because the accompanying symptoms of anorexia and vomiting are also characteristic symptoms of many other ills of infancy.

*Source: Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.: Diabetes *8*:289, 1959.

for those pediatric puzzlers..."A routine urinalysis and blood sugar should be done whenever the possibility of diagnosing diabetes is entertained."*

DIABETES MELLITUS AT AGES 1 TO 5

Order of Frequency of Presenting Symptoms in 110 Patients

Symptoms	No. of Patients	Per cent of total group
Polyuria	93	84.5
Polydipsia	89	81.0
Weight loss	47	42.7
Polyphagia	28	25.4
Anorexia	16	14.5
Lethargy	14	12.7
Enuresis	7	6.4
Vomiting	5	4.5
Irritability	3	2.7
"Craving for sweets"	3	2.7
"Sticky diaper"	3	2.7
"Strong odor to urine"	2	1.8
Glycosuria	2	1.8
Hypoglycemia	2	1.8
Personality change	1	0.9
Boils	1	0.9
Headache	1	0.9
Abdominal cramps	1	0.9

Adapted from Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.*

the standardized urine-sugar test for reliable quantitative estimations

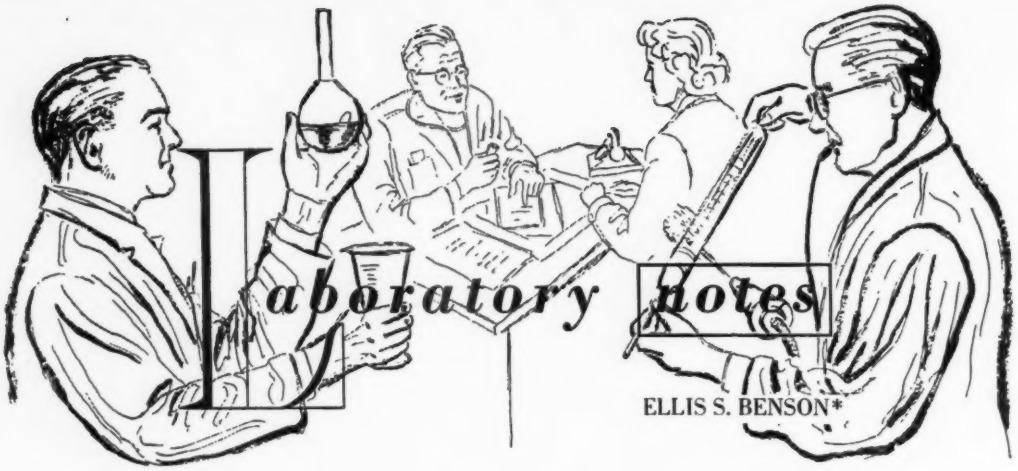
AMES COMPANY, INC. Elkhart • Indiana Toronto • Canada

COLOR-CALIBRATED CLINITEST®

BRAND Reagent Tablets

84060

- **full-color calibration, clear-cut color changes**
- **established "plus" system covers entire critical range**
- **standard blue-to-orange spectrum**
- **standardized, laboratory-controlled color scale**
- **"urine-sugar profile" graph for closer control**



ELLIS S. BENSON*

New Interest in Urine Sugars Other Than Glucose

K. M. K. was the first child of normal, healthy adults. She weighed 7 lb. at birth and, although normal in appearance, had persistent regurgitation and stools which contained undigested food. Jaundice was first noted on the fourth day of life and persisted for three weeks. She was irritable, slept poorly, and failed to gain weight. Because of these symptoms, she entered the hospital at the age of two months at which time she weighed 8 lb. The liver was enlarged and firm; its edge was palpable 5 cm. below the right midcostal line. There was bilateral lenticonus but no cataracts.

The most striking laboratory finding was 3 plus urine sugar, using the Benedict qualitative test, despite a negative test using glucose oxidase test papers.† Thus, the urine sugar was not glucose. Its identity was established as galactose by using chemical tests. Because of this finding, a galactose tolerance test was performed. Galactose, 1.75 gm. per kilogram of body weight, was given by mouth, and in two hours the concentration in the blood had risen to 380 mg. per cent. In five hours, the level was still 280 mg. per cent. Blood glucose, on the other hand, remained constant at 60 mg. per cent for two hours and then fell to 30 and 20 mg. per cent at three and four hours, respectively. These results were typical for those of congenital galactosemia. The patient was placed on a milk-free diet on which she thrived. The lenticonus gradually improved and she gained weight and grew impressively. When last seen at the age of seven years, her physical development was normal, although the liver was still slightly enlarged, and intelligence tests showed a mental retardation of one and one-half years.

T. K., the younger sister of K. M. K., weighed 7 lb. at birth, and appeared to be normal. Urine examination for galactose, car-

(Continued on page A-37)

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

†CLINISTIX®, a product of Ames Company, Inc., Elkhart, Indiana; TES-TAPE®, a product of Eli Lilly and Company, Indianapolis.

ried out immediately because of the family history, was positive. She was placed on a milk-free diet. Later a galactose tolerance test was performed with results similar to those obtained in the case of K. M. K. When last seen at the age of five years, her physical development was normal. She appeared well nourished, had no liver enlargement or abnormal ocular findings, and intelligence tests indicated a higher than normal intelligence.

These two sisters are the victims of a very interesting congenital disturbance called galactosemia, a disturbance in the ability to metabolize galactose. This disturbance is of interest for a number of reasons, on each of which I will comment briefly. (1) It is a striking example of a congenital defect in which results are very damaging, but which can be readily and completely averted if the diagnosis is made early (as in the case of T. K.) and can even be reversed to some extent later (as in the case of K. M. K.). (2) It is a sterling example of what is now being described as a "molecular defect," that is, a clinical disturbance resulting from the loss of or defect in one species of molecule. (3) It exemplifies the unfortunate corollaries that may accompany advances in laboratory methods.

In the past, the presence of reducing sugars other than glucose in the urine has frequently been taken lightly. These obscure meliturias have been considered to be so rare or benign that they are of little or no clinical significance. While this may still be true of fructosuria and pentosuria (see below), it is not true of galactosuria. Significant galactosuria occurs only in congenital galactosemia, a condition which is far from benign and is not as rare as was once thought. Affected infants usually appear normal at birth, but after a few days of milk feeding, there are such symptoms as vomiting, lethargy, failure to gain weight, and enlargement of the liver and jaundice.[1] In severe cases, death occurs early. Milder cases in which the patients survive may be unrecognized until severe mental retardation has developed or cataracts have formed. A striking feature of the disease is its reversibility on exclusion of galactose from the diet if the diagnosis is made early.

Lactose is a disaccharide made up of glucose and galactose joined in β linkage. It is essentially the sole source of galactose in the diet, and in turn is found almost exclusively in milk and milk products. When these are excluded from the diet, signs and symptoms are promptly reversed, and rapid weight gain and physical growth ensue. Unfortunately, mental retardation once established does not seem to reverse itself, underscoring forcefully the importance of early diagnosis.

Galactose, after its absorption from the gastrointestinal tract, is transported to the liver, where it is converted to glucose and enters into the general "glucose pool." At least five enzymatic reactions take place in sequence in this conversion and these are described in a recent review by Isselbacher.[2] Kalckar, Anderson and Isselbacher[3, 4] have shown that in congenital galactosemia the defect is specifically localized to one of these enzymes: galactose-1-phosphate uridyl transferase (Gal-1-P uridyl transferase). Red blood cells and liver of affected individuals are deficient in this crucial enzyme activity. The clinical signs and symptoms of the disease can be explained most satisfactorily by a cytotoxic effect of galactose accumulation in brain, lens and liver. In adolescence, an alternate route for disposal of galactose becomes prominent, and the consequences of lack of the transferase diminish.[2]

Clearly, early diagnosis is of paramount importance to successful management of galactosemia. A simple means of screening newborn infants for this condition is distinctly needed.

Glucose oxidase test papers have gained wide use recently in screening urines for the presence of sugar. These test papers provide a simple, rapid, sensitive and specific test for glucose. One must keep in mind, however, that since these test papers are specific for glucose, galactose will give negative results; if this is the only method used to screen urine sugars, galactosuria will be missed. On the other hand, a method which tests the reducing ability of sugars, such as the qualitative Benedict test,[5] will detect both glucose and galactose. If one uses this type of test for a reducing sugar to screen the urine of infants

(Continued on page A-38)

TABLE 1

SIMPLE MEANS FOR SEPARATELY IDENTIFYING FOUR URINE SUGARS*

URINE SUGAR	BENEDICT'S QUALITATIVE TEST			GLUCOSE OXIDASE TEST PAPERS
	25° C. for 3 hr.	*50° C. for 30 min.*	*100° C. for 5 min.*	
Glucose	0	0	+	+
Galactose	0	0	+	0
Fructose	0	+	+	0
Xyloketose	+	+	+	0

*Using rate of reduction of copper in Benedict's qualitative sugar reagent as a function of temperature and time (+ result = formation of yellow precipitate) and glucose oxidase test papers.

and checks all positive results with glucose oxidase test papers, one has an ideal method of picking up not only glucosuria but also galactosuria and other meliturias as well (table 1). The combination of a positive Benedict test and a negative glucose oxidase test is suggestive evidence of the presence of sugar other than glucose, and galactosuria should be suspected. Positive identification is now most readily and simply accomplished by the use of one-dimensional paper chromatography[6] (figure 1).

The galactose tolerance test[7] may be used as it was in the two illustrative cases. However, it has these disadvantages: (1) It is cumbersome, since it requires the separate determination of glucose and galactose, usually by using a copper-reducing method before and after yeast fermentation of glucose; (2) it may not be entirely without hazard to the patient.[2] Serious reactions such as generalized convulsions may occur (note the hypoglycemia which occurred in patient K. M. K.). Recently, a method using galactose oxidase has been reported,[8] and this method is promising since it will permit rapid specific identification of galactose, but as yet the enzyme is not generally available.

The most specific currently available method of diagnosis of galactosemia is through assay of the enzyme system Gal-1-P uridyl transferase in red blood cells.[9] This method also avoids the hazards involved in the administration of galactose.

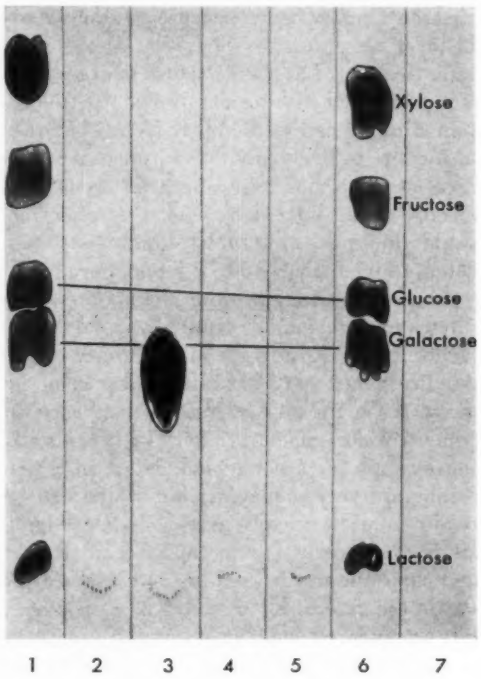


FIGURE 1. Paper chromatogram. Columns 1 and 6 contain 100 μg. each of pure xylose, fructose, glucose, galactose and lactose. Columns 2, 4, 5 and 7 represent normal urines and column 3 the urine of a patient with congenital galactosemia.

Reproduced from the *Archives of Disease in Childhood*.[6]

Pentosuria has been of interest chiefly as a medical curiosity. The diagnosis usually is made in normal individuals who give evidence of a reducing sugar in the urine on examination for life insurance policies. Attempts have been made to associate this finding with a number of clinical syndromes, but the consensus now holds that the condition is a hereditary one without physiologic penalty.[10] This circumstance is especially fortunate in the light of the ubiquity of pentoses and pentosans in the human diet.

The identity of the pentose has been a subject of controversy, but this seems to be now resolved in favor of xyloketose.

Similarly, no adverse metabolic conse-

(Continued on page A-41)

quences are associated with essential fructosuria. Probably both of these conditions, essential pentosuria and fructosuria, have much in common with renal glycosuria and are related to abnormalities in the renal tubular transport of sugars.

Ketoses, such as xyloketose and fructose, reduce copper more rapidly than do aldoses, such as glucose and galactose. This characteristic may be used to identify them by incubating the urine with Benedict's qualitative sugar reagent at three temperatures for varied periods of time[11] (table 1). Xyloketose may be identified further using Bial's reagent,[5] and fructose by the Seliwanoff test.[5] Both fructose and xyloketose can be readily identified by simple one-dimensional paper chromatography[6,12] (figure 1).

REFERENCES

1. Ritter, J. A. and Cannon, E. J.: Galactosemia with cataracts. New England J. Med. 252:747, 1955.
2. Isselbacher, K. J.: Galactose metabolism and galactosemia. Am. J. Med. 26:715, 1959.
3. Kalckar, H. M., Anderson, E. P. and Isselbacher, K. J.: Galactosemia, a congenital defect in a nucleotide transferase. Biochim. et biophys. acta 20:267, 1956.
4. Anderson, E. P., Kalckar, H. M. and Isselbacher, K. J.: Defect in the uptake of galactose-1-phosphate into liver nucleotides in congenital galactosemia. Science 125:113, 1957.
5. Melby, J. C., Benson, E. S. and Ohlen, M.: Urinalysis. In Watson, C. J. (ed.): Outlines of Internal Medicine. Ed. 9. Dubuque, Iowa, Wm. C. Brown Co., 1958, part V, pp. 537-539.
6. Bickel, H. and Hickmans, E. M.: Paper chromatographic investigations on urine. Arch. Dis. Childhood 27:348, 1952.
7. Townsend, E. H., Mason, H. H. and Strong, P. S.: Galactosemia and its relation to Laennec's cirrhosis: Review of literature and presentation of six additional cases. Pediatrics 7:760, 1951.
8. Cooper, J. A. D., Smith, W., Bacila, M. and Medina, H.: Galactose oxidase from *Polyporus circinatus, Fr.* J. Biol. Chem. 234:445, 1959.
9. Anderson, E. P., Kalckar, H. M., Kurahashi, K. and Isselbacher, K. J.: A specific enzymatic assay for the diagnosis of congenital galactosemia. J. Lab. & Clin. Med. 50:469, 1957.
10. Touster, O.: Pentose metabolism and pentosuria. Am. J. Med. 26:724, 1959.
11. Lasker, M. and Enklewitz, M.: A simple method for detection and estimation of L-xyloketose in urine. J. Biol. Chem. 101:289, 1933.
12. Wright, S. W., Ulstrom, R. A. and Szewczak, J. T.: Studies on carbohydrates in body fluids. I. Identification by means of paper chromatography. A.M.A. J. Dis. Child. 93:173, 1957.

(Advertisement)

Maintenance of Capillary Integrity

Incidence of impaired capillary function is more frequent than previously recognized. Many publications indicate the frequency of increased capillary weakness ranges from 16% to as high as 80% of patients examined (1-4).

Reports show older people have a high incidence of capillary fragility (6). In a group of 111 patients, capillary weakness was noted to be greatest in the fifth and sixth decades (5).

Hypertensives (7, 8, 9) and those with chronic diseases such as arteriosclerosis, diabetes and rheumatoid arthritis, have shown varying degrees of capillary involvement. Hemorrhagic conditions of the brain and heart have shown localized injury in the capillary (10, 11).

Capillary fragility has been shown to be associated with many bacterial, viral and inflammatory diseases (12-23).

Various bioflavonoid materials have been evaluated for their effect upon the capillary. Degree of fragility has been determined by numerous procedures (24-30).

The therapeutic rationale of combining *Hesperidin* or other *citrus bioflavonoids* with ascorbic acid or other therapeutic agents is based on the premise that capillary weakness may be a contributing factor to the disease state and that capillary integrity should be maintained. *Citrus bioflavonoids* in conjunction with ascorbic acid appear to enhance the efficacy of other therapy, and help control such factors as infection, stress and nutritional deficiency even in cases not showing capillary weakness.

NOTE: For bibliography (B-701) write Sunkist Growers, Pharmaceutical Division, 720 E. Sunkist Street, Ontario, California.

reaches
all nasal
and paranasal
membranes
systemically[1]

Pharmacologically balanced formula for prompt symptomatic relief

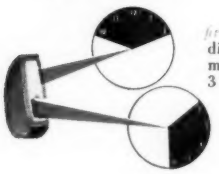
- in nasal and paranasal congestion
- in sinusitis and postnasal drip
- in allergic reactions of the upper respiratory tract

Triaminic[2,3] is safer and more effective than topical medication

- transported systemically to *all* respiratory membranes
- provides longer-lasting relief
- presents no problem of rebound congestion
- avoids "nose drop addiction"

1. Fabricant, N. D.: E.E.N.T. Monthly *37*:460 (July) 1958.
2. Lhotka, F. M.: Illinois M. J. *112*:259 (Dec.) 1957.
3. Farmer, D. F.: Clin. Med. *5*:1183 (Sept.) 1958.

Relief is prompt and prolonged because of this special timed-release action:



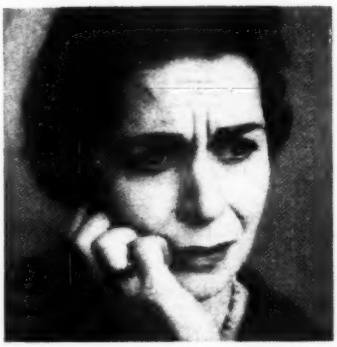
first — the outer layer dissolves within minutes to produce 3 to 4 hours of relief

then — the core disintegrates to give 3 to 4 *more* hours of relief

the leading oral nasal decongestant

the common problem basically unresponsive to tranquilizers

TYPICAL CASE HISTORIES FROM THE LITERATURE



"A 44-year-old housewife with symptoms of anxiety referable to her heart and stomach. All examinations were negative for the presence of organic disease... she had received 4 different tranquilizers."

On Nardil "the majority of her anxiety symptoms had disappeared. Later she remarked that she was 100% better....There has been no return of former complaints."*

*Hobbs, L. E.: *Virginia Med. Monthly* 86:692, 1959.

"Characteristically the patient complains of impaired appetite, insomnia, irritability, loss of attention and concentration, tendency to worry and marked irritability... treatments are usually built [in vain] around some sedative or tranquilizer....

With Nardil this condition is easily managed... by the practicing clinician."**

**Sainz, A.: *Dis. Nerv. System* 20:537, 1959.

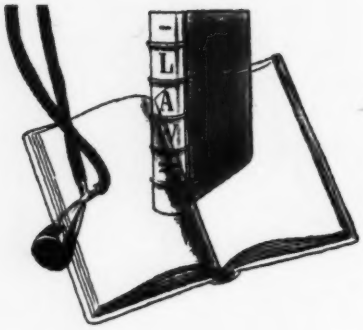
simple, economical, rapidly effective therapy

WARNER CHILCOTT
MORRIS PLAINS, N.J.

DOSAGE: 1 tablet three times a day.

SUPPLIED: Orange-coated tablets, each containing 15 mg. of phenylethylhydrazine present as the dihydrogen sulfate. Bottles of 100.

NA-6P03



Forensic Medicine

Reviews of Recent Books

► THE LAW OF MEDICAL PRACTICE

By Burke Shartel, Professor of Law, and Marcus L. Plant, Professor of Law, University of Michigan, Ann Arbor. 445 pages. 1959, Charles C Thomas, Springfield, Illinois. $12.50.

This book is an anthology of the law as applied to the healing arts. Great use has been made of the medicolegal cases briefed by the law department of the American Medical Association and the American Law Reports Annotated. The advice and opinions on the law are based primarily on the citations from those sources. As much space is given to footnotes as to text. The bibliography following each chapter is full and detailed.

The authors state that their purpose, as applied to the medical profession, is to "meet the daily need of the established practitioner, to keep the doctor out of trouble." Although the book was written primarily for doctors and secondarily for lawyers, the goal has been achieved, but in the reverse order. From a lawyer's point of view, there is a rich source of fundamental material in the footnotes and bibliography. It is difficult to envision a busy doctor, who finds so little time to read the necessary medical literature, having time for this type of reading. However, it would be invaluable as a reference book.

There are eight chapters, a number of which seem to be unnecessary, namely: chapter 5, dealing with licensure; some sections of chapter 7, particularly the material on reports and services and the criminal liabilities of the physician, which should be so obvious to the practicing physician as to be mere surplusage, and chapter 8, "Operation of the legal system."

When the authors adhere to their script, they do a workmanlike job. However, when they start offering opinions on the "Battle of the experts and modern reforms," they lose their objectivity. Nevertheless, this monumental work is a valuable reference book for the lawyer and physician interested in the law of medical practice.

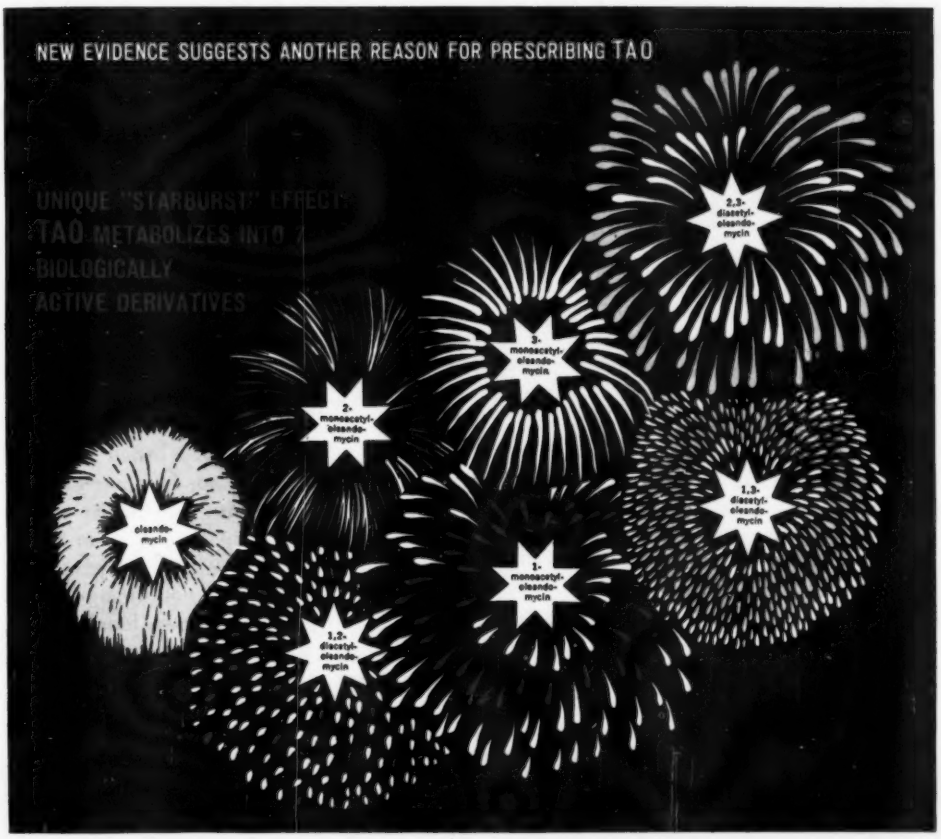
JACK L. SACHS, LL.B.

► THE PHYSICIAN AND THE LAW

By Rowland H. Long, Assistant Professor in Forensic Medicine, New York University Post-Graduate Medical School, New York. Ed. 2. 302 pages. 1959, Appleton-Century-Crofts, Inc., New York. $5.95.

The author of this most readable volume has the happy faculty of writing simply, yet fluently. It is no chore to read several chapters of "The Physician and the Law" at a sitting. Because Mr. Long uses frequent examples taken from actual court decisions, this read-

(Continued on page A-60)



The impression that TAO is an unusually active antibiotic has steadily gained recognition by impressive clinical performance. Now come reports of **in vivo** and **in vitro** biological and biochemical evaluations that show TAO to be indeed unique.[1,2]

TAO differs from other antibiotics in that it is metabolized to multiple active compounds which **remain** active throughout their presence in the body. These 7 derivatives (in addition to TAO) show activity against common Gram-positive pathogens, including resistant strains of **Staph. aureus.**

In light of these findings, take another look at TAO performance: • 92% success in published cases of Gram-positive respiratory, skin, soft tissue and genitourinary infection • Effective against 78% of 64 "antibiotic-resistant" epidemic staphylococci. (In the same study, chloramphenicol was active against 52%; erythromycin against only 25%)[3] • No side effects in 94%; infrequent reactions mild and easily reversed • Quickly absorbed • Highly palatable.

Sound reasons to: Start with TAO to end 9 out of 10 common Gram-positive infections.

Supplied: TAO Capsules—250 mg., and 125 mg., bottles of 60. **TAO for Oral Suspension**—125 mg. per tsp. (5 cc.) when reconstituted; unusually palatable cherry flavor; 60 cc. bottle. Prescription only.

Other TAO forms available: TAO Pediatric Drops: flavorful, easy to administer. **TAO®-AC:** TAO analgesic, antihistaminic compound. **TAOMID®:** TAO with triple sulfas. **Intramuscular or Intravenous:** in clinical emergencies. Prescription only.

1. English, A. R., and McBride, T.: J. Proc. Soc. Exper. Biol. & Med. 100:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. 8:420 (Aug.) 1958.

designed for superior control of common Gram-positive infections

TAO®

(triacetyloleandomycin)
Capsules/Oral Suspension

℞ only

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

Forensic Medicine

ing is not sterile. One can easily comprehend what has been read.

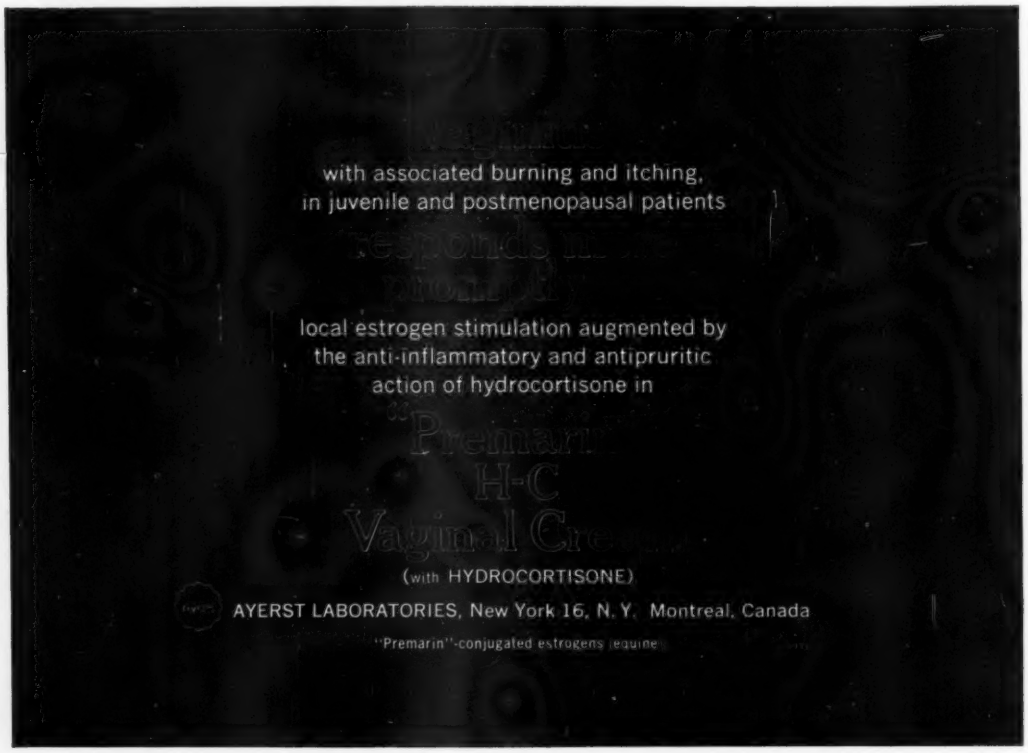
The preface states that the book's purpose is to afford the practicing physician some knowledge of the rules of law which govern his conduct in the physician-patient relationship and to help the physician who is called on to be a witness in a court proceeding. This is a broad undertaking and, admittedly, no single book on such broad and important subjects could accomplish such high purposes to everyone's satisfaction. Mr. Long, however, has made a significant contribution and approaches his purposes well. The end result is a lucid, helpful explanation of principles of law as applied to the practice of medicine.

Among the subjects discussed are malpractice and insurance; artificial insemination and adoption; autopsies and abortions; procedures for commitment of the mentally ill, and the like. When necessary, as in discussion of malpractice, the author discusses conflicting legal opinions and comments on their relative validity. He exercises commendable restraint in discussing statutes which may require affirmative action by the doctor (e.g., carrying workmen's compensation insurance to cover aides, assistants, technicians, etc.). He points out that laws differ from state to state, and he then offers concrete suggestions so that the reader may acquire necessary knowledge of the law in his own state.

The author devotes several chapters to medicine and criminal law, to forensic medicine. Too frequently, the physician's obligations, rights and duties in this area are treated lightly or overlooked. And he devotes several chapters to the subject of the doctor as a witness, using helpful examples.

Only one *caveat* needs be mentioned. This is a general treatment of a broad subject. The book was not written nor is it intended to answer specific questions. The reader may read and understand, he may acquire an appreciation of the philosophy of law and general principles of law. He should not attempt, however, to take the law into his own hands or to use this book as a substitute for competent, personal legal advice in specific instances.

EDWIN J. HOLMAN, L.L.B.


with associated burning and itching,
in juvenile and postmenopausal patients
local estrogen stimulation augmented by
the anti-inflammatory and antipruritic
action of hydrocortisone in
(with HYDROCORTISONE)
AYERST LABORATORIES, New York 16, N. Y. Montreal, Canada
"Premarin"-conjugated estrogens (equine)

Radiology FOR PRACTICING PHYSICIANS

Roentgen Diagnosis of Lesions of the Esophagus, Part 1

JAMES R. WILLIAMS AND PAUL C. HODGES*

University of Chicago, Chicago

Dr. James R. Williams received his M.D. degree from the University of Tennessee College of Medicine in 1949. Following a brief period of general practice, he entered the United States Air Force for two years. He served a one year residency in internal medicine before beginning his radiology residency at the University of Chicago in 1954. Following the completion of his residency training, he remained at the University of Chicago, with a current appointment as Assistant Professor in the Department of Radiology. He is a diplomate of the American Board of Radiology.—Paul C. Hodges, M.D.

JAMES R. WILLIAMS

SIGNIFICANT abnormalities of the esophagus usually produce symptoms early in their course of development. The x-ray examination serves to confirm the presence of lesions suspected clinically, to demonstrate the location and extent of the pathologic state, and, in most cases, to provide reasonably reliable information regarding the type of pathologic condition that is present. Esophagoscopy, biopsy or exfoliative cytology may be necessary in order to establish a precise pathologic diagnosis.

*Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

Indentations and Displacements

The esophagus normally is indented by three structures. The aortic arch pushes it to the right and posteriorly, the left main stem bronchus indents the anterior surface slightly, and the diaphragm makes a circular construc-

FIGURE 1. Displacement by large left auricle. Rheumatic mitral stenosis with enlargement of the left auricle and compression and backward displacement of the esophagus.

tion. Primary or metastatic mediastinal tumors may compress or displace the esophagus, and the enlarged left atrium of mitral disease or certain congenital cardiac lesions may compress it and displace it posteriorly just below the carina (figure 1). Enlargement of either the left or right ventricle may displace the lower esophagus posteriorly, and a dilated, tortuous descending thoracic aorta may displace it anteriorly and to the right just above the diaphragm.

Congenital Malformations

Atresia of the esophagus, with or without tracheoesophageal fistula, is a serious congenital malformation which is suspected when newborn infants aspirate and become cyanotic at the time of the first feeding. In the most common type a dilated proximal esophagus terminates above the level of the carina as a blind pouch, and a fistula connects the trachea or a major bronchus to the lower esophagus below the site of atresia. The condition is diagnosed by demonstrating a blind esophageal pouch in an infant who has air in the stomach, small bowel or colon (figure 2a). Attempts to visualize the tracheoesophageal fistula with contrast material are unnecessary and merely add to the respiratory distress caused by the inevitable aspiration pneumonia. In the next most common type there is atresia without tracheoesophageal fistula. This is diagnosed by finding a blind upper esophageal pouch in an infant who has no air in the gastrointestinal tract (figure 2b and c). Rarely there may be atresia with a fistula from the tracheobronchial tree above the defect and with or without a second fistula from the tracheobronchial tree to the esophagus below the atresia. Tracheoesophageal fistula without esophageal atresia does occur, but its incidence is not known because the condition is difficult to demonstrate by x-ray or to find at surgery or autopsy (figure 3).

A right-sided aortic arch usually displaces the esophagus anteriorly and to the left, but produces no symptoms (figure 4). A double aortic arch or a tightly stretched ligamentum arteriosus, usually in association with a right-sided aortic arch, may produce a ring which compresses the trachea and esophagus. This is called a "vascular ring" and is usually detected in young infants because of symptoms of tracheal compression (figure 5).

Diverticula

Zenker's pulsion diverticula arise from the posterior wall of the hypopharynx in the midline at the decussation of the fibers of the cricopharyngeus muscle as a result of a congenitally weak point which gradually is enlarged by hypopharyngeal pressure generated by deglutition. These diverticula produce a sensation of fullness in the neck after eating and, if very large, they may produce a visible mass. The patients frequently regurgitate undigested food and may have repeated episodes of pneumonia from aspiration during sleep. Zenker's diverticula vary in size from 1 to 2 mm. to 10 cm. or more. The larger diverticula displace the esophagus anteriorly and compress it to a marked degree (figures 6 and 7).

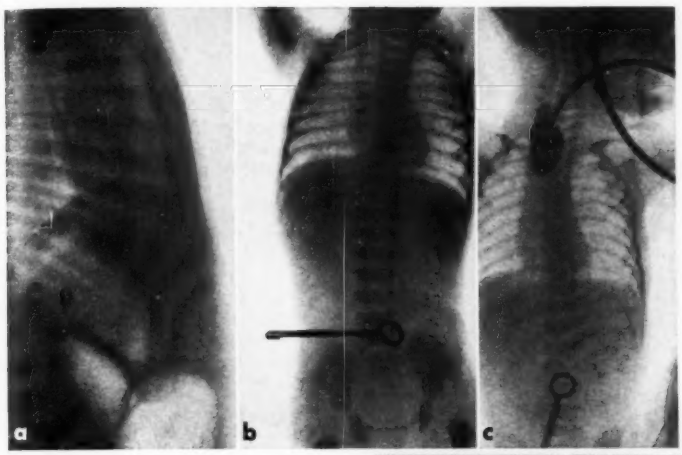


FIGURE 2. Esophageal atresia.

a. Atresia with fistulous communication between trachea and lower esophagus. Upper esophageal blind pouch filled with barium; stomach and colon contain air as a result of the tracheal fistula.

b and c. Atresia without fistula; (b) upper esophageal pouch filled with air, (c) with barium. No air in alimentary tract.

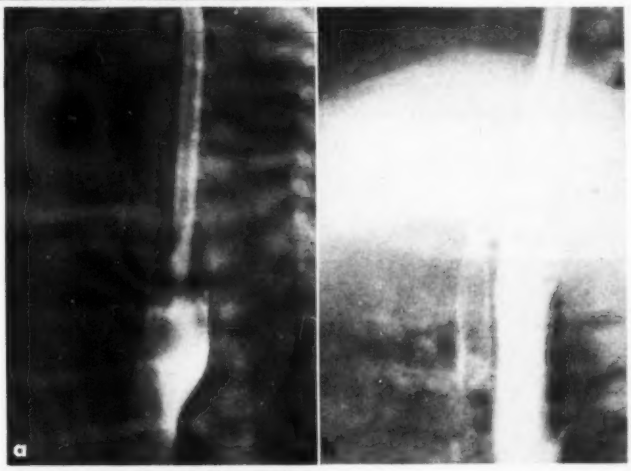


FIGURE 3. Tracheoesophageal fistula without atresia.

a. As soon as a small amount of barium is introduced into the esophagus through a catheter, some of it leaks into the trachea where it coats and thus renders visible the tracheal mucosa.

b. With the injection of more barium into the esophagus, a tiny 1 mm. fistulous tract is demonstrated and considerable barium passes into the tracheobronchial system.

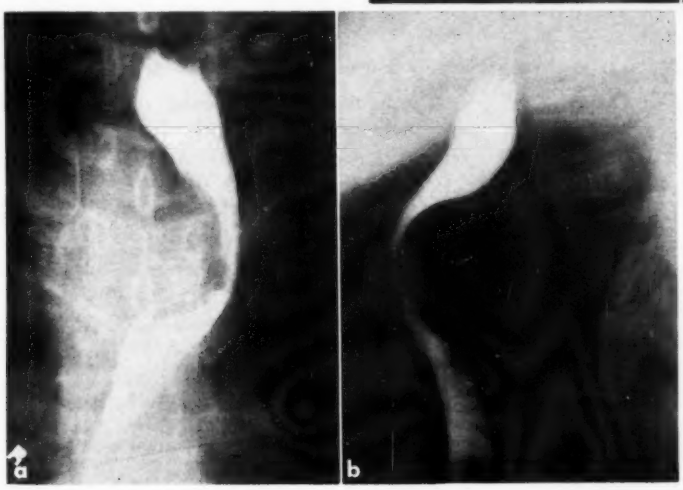


FIGURE 4. Displacement of esophagus by anomalous right-sided aortic arch.

a. In the frontal view, the esophagus is displaced to the left.

b. In the lateral view, displacement is anterior. Note also the deformity of bodies of thoracic vertebrae caused by pressure from the anomalous arch.

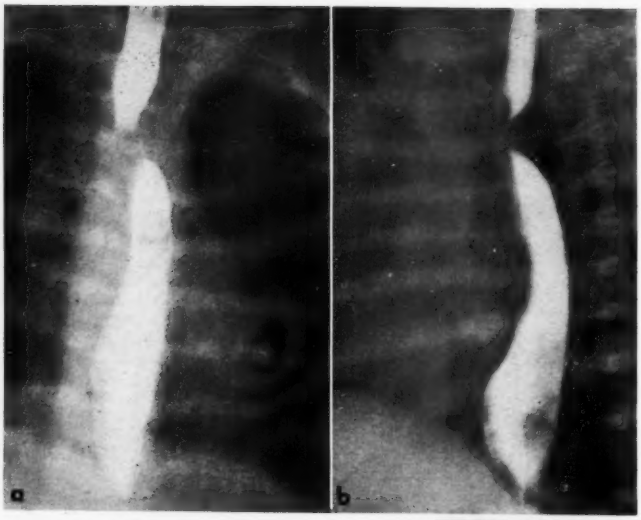


FIGURE 5. Anomalous "vascular ring" pinching trachea and esophagus down until only slitlike lumens remain at the point of pressure.

a. Frontal view.

b. Lateral view.

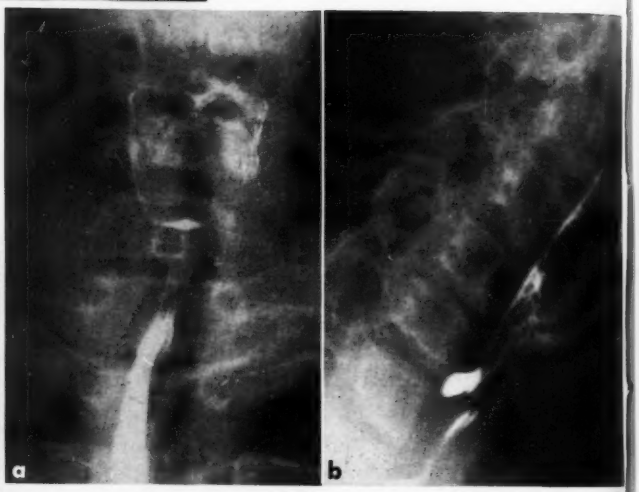


FIGURE 6. Small Zenker's diverticulum.

a. In the frontal projection, a diverticulum as small as this is easily overlooked.

b. In the lateral view, however, the small diverticulum is easy to see. It springs from the posterior wall at the junction of the hypopharynx and esophagus and is directed backward toward the spine.

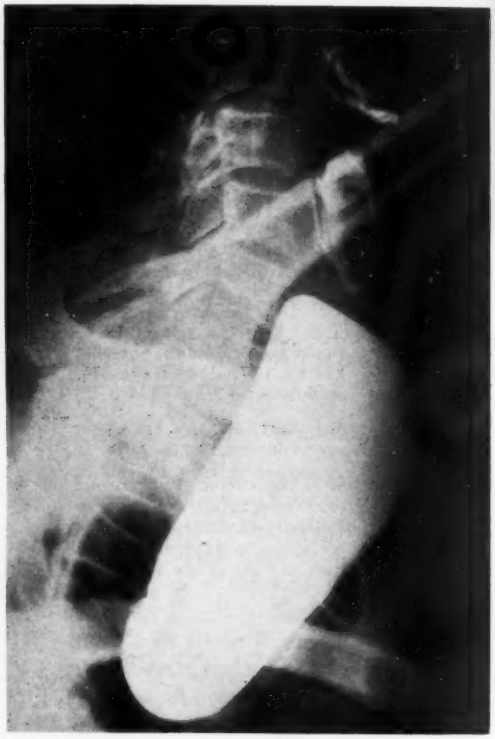


FIGURE 7. Large Zenker's diverticulum. This enormous diverticulum, which measures more than 5 by 12 cm. in diameter, pushes the esophagus far anterior and compresses it.

FIGURE 8. Large diverticulum springing from the right side of the lower esophagus. Above diverticulum is the normal esophagus; below and to the left are the fundus and body of the stomach.

FIGURE 9. Hiatus hernia.

a. Herniation of a large portion of the fundus of the stomach through the hiatus (lateral view).

b and c. Herniation of the cardioesophageal junction through the hiatus. In (b), see narrowing of the lower esophagus as a result of peptic esophagitis; in (c), an ulcer crater may be seen at the site of narrowing.

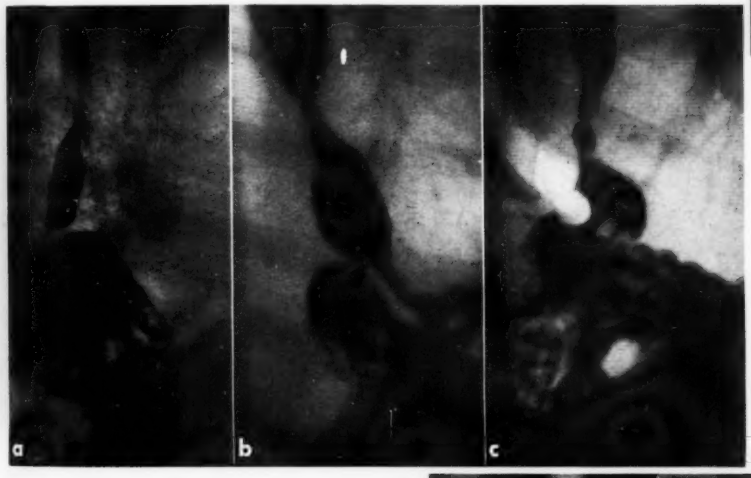


FIGURE 10. Phrenic ampulla. This bulbous enlargement of the lower end of the esophagus is a normal anatomic variant.

a. At beginning of Valsalva exercise, barium has begun to reflux into the upper esophagus.

b. A few seconds later, with continued effort; more reflux has occurred.

c. Still later and with continued Valsalva exercise, the ampulla has emptied almost completely by reflux into the proximal esophagus.

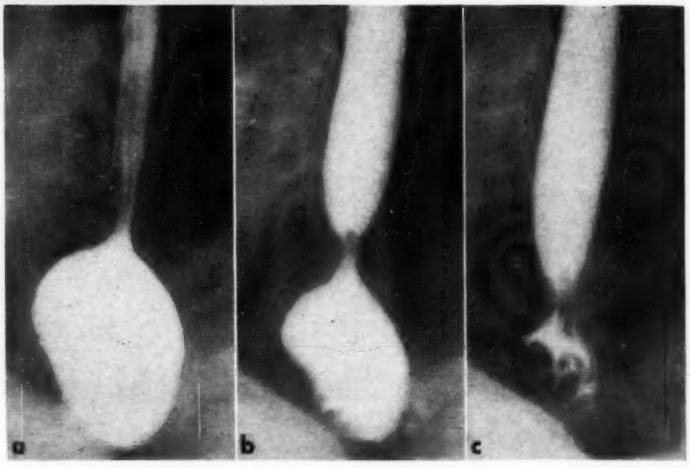
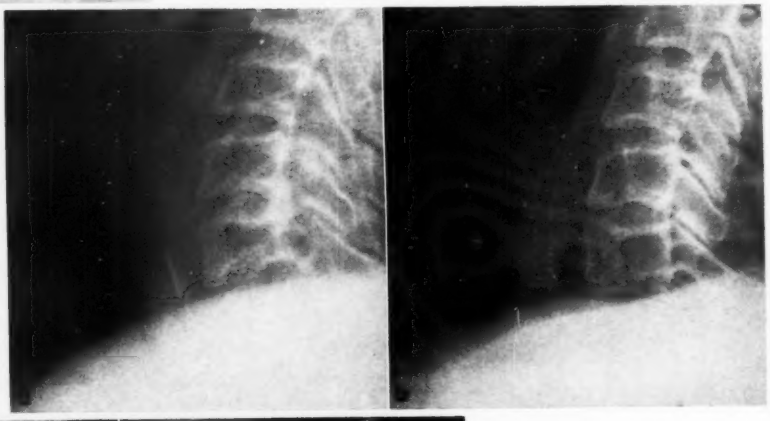


FIGURE 11. Lower esophageal ring. A symptomless complication of a symptomless phrenic ampulla.

FIGURE 12. Chicken bone in esophagus.

a. Lateral view. The little splinter of bone shows faintly in the space between the posterior wall of the trachea and the body of the sixth cervical vertebra at a point just above the dense shadow of the patient's shoulder.

b. Following surgical removal of the splinter.



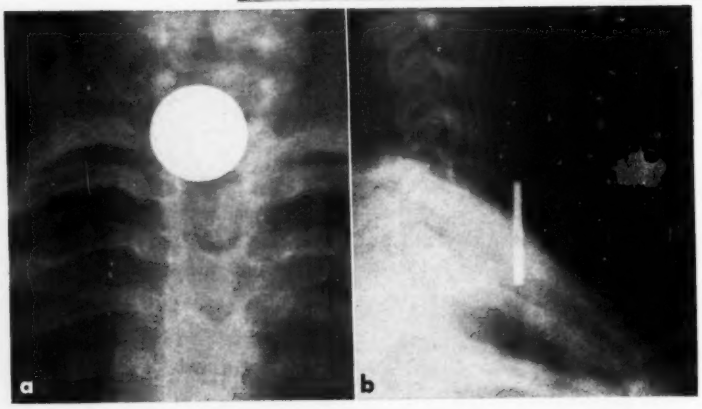


FIGURE 13. Coin in esophagus, frontal (a) and lateral (b) views. The posterior position and the alignment of the face of the coin perpendicular to the sagittal plane establish the fact that it is in the esophagus. If it were in the trachea, the surface of the coin would be parallel to the sagittal plane of the body.

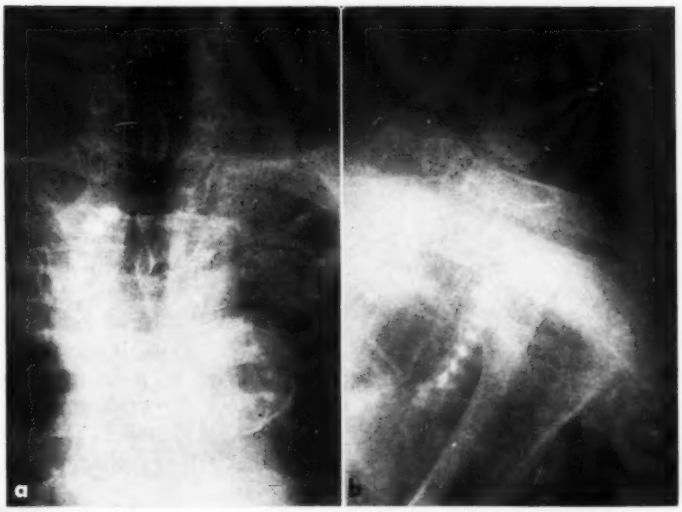


FIGURE 14. Dental prosthesis in esophagus, frontal (a) and lateral (b) views. The prosthesis, identified by seven clumps of metal, has lodged at the level of the aortic arch.

FIGURE 15. Peach seed in esophagus. A large lens-shaped radiotranslucent peach seed which has lodged in the upper esophagus is rendered visible by surrounding barium.

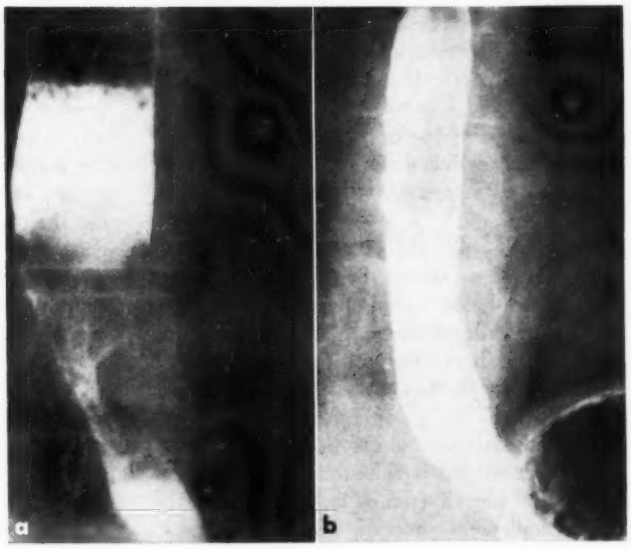


FIGURE 16. Piece of meat lodged in the lower esophagus.

a. Obstruction was not complete and so ingested barium leaked past the obstruction, visualizing both the proximal and distal ends of the foreign body.

b. Following surgical removal, the esophagus is normal.

FIGURE 17. Lye stricture. Typical fusiform narrowing of esophagus. Appearance 40 years after the ingestion of lye. Subsequently, squamous-cell carcinoma developed at the site of stricture.

Symptomless small diverticula frequently occur in the middle and lower thirds of the esophagus. The most common location is just below the aortic arch at the level of the carina and in this location scarring from inflammatory pulmonary disease may be a causative factor. Larger diverticula located in the lower third may cause minor symptoms (figure 8).

Diaphragmatic Hernia

Herniation of any of the abdominal viscera may occur through any of the natural openings in the diaphragm. The most common form is the herniation of a portion of the stomach through the esophageal hiatus. When a portion of the gastric fundus herniates through the hiatus and lies beside the esophagus, the condition is called eccentric or paraesophageal hernia (figure 9a), and when the cardioesophageal junction herniates through the hiatus, it is called a concentric hernia (figure 9b and c).

The so-called congenital short esophagus type of hiatus hernia probably is not of congenital origin but is rather a concentric hernia in which superimposed peptic esophagitis produces esophageal shortening. Normal ballooning of the distal 4 or 5 cm. of the esophagus above the diaphragm, known as the "phrenic ampulla," must be differentiated from a hiatus hernia (figure 10). The ampulla may be of considerable size, particularly if the patient swallows, then inspires deeply, closes the glottis and strains. This maneuver prevents the esophagus from emptying through the cardia, and as the contraction wave travels down the esophagus the ampulla distends.

The x-ray diagnosis of esophageal hiatus hernia should be reserved for those cases in which definite gastric rugae can be demonstrated to lie above the diaphragm. A transverse constriction frequently seen in the midportion of a distended phrenic ampulla has been termed a "lower esophageal ring" (figure 11). Whether or not this ring is capable of producing clinical symptoms remains controversial. The one reported autopsy of a patient with a radiologically demonstrated ring showed a small hiatus hernia with the esophagogastric mucosal junction at the site of the ring.

Foreign Bodies

If a swallowed foreign body is able to pass from the pharynx through the constriction produced by the cricopharyngeus muscle, usually it passes on through the esophagus into the stomach. Occasionally, a foreign body becomes arrested in the esophagus, even without the presence of underlying esophageal disease. If a patient is known to have swallowed an x-ray-opaque foreign body and symptoms suggest that it has become lodged in the pharynx or esophagus (figures 12, 13 and 14), frontal and lateral films should be made. Foreign bodies opaque enough to be seen by this technic include beef and pork bones, most fowl bones, metallic objects and most glass. If the foreign body is not visible on the films (figure 15), it is probably wisest to resort at once to esophagoscopy rather than to x-ray

examination of the esophagus, because the barium required for such an examination may obscure small foreign bodies at subsequent esophagoscopy. The substitution of aqueous organic iodine compounds for barium eliminates this objection but, unfortunately, such material seldom coats the mucosa sufficiently well to demonstrate small foreign bodies. A foreign body impacted in the esophagus may produce marked, persistent contraction which may be mistaken for an organic stricture of the esophagus. Following removal of the foreign body, the examination may show a perfectly normal esophagus (figure 16).

Ingestion of Caustic Substances

The ingestion of caustic substances produces an erosive esophagitis in an area of one of the natural constrictions of the esophagus with eventual scarring and stricture. By x-ray one sees a smoothly tapering stricture, usually at the level of the aortic arch or just above the diaphragm. Patients with lye strictures of the esophagus have an increased tendency to develop esophageal carcinoma (figure 17).

If you *Change*

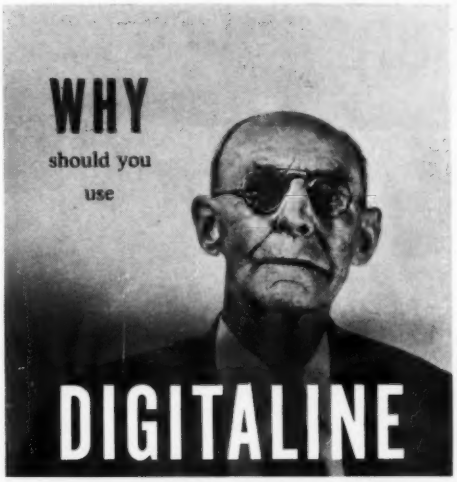
YOUR ADDRESS

Won't you please notify us as far in advance as possible. Send your old address together with the new.

Copies mailed to your old address will not be forwarded by the Post Office unless you provide the Post Office with the forwarding fee.

Send your change of address to

POSTGRADUATE MEDICINE
Essex Bldg., Minneapolis 3, Minn.



NATIVELLE®

the original crystalline digitoxin

BECAUSE it assures you of . . .

Flexibility of Administration—Digitaline Nativelle provides for rapid oral digitalization within a convenient range of tablet strengths. When desired the intravenous route, or the new intramuscular injection may be employed. The essentially non-alcoholic intramuscular formula, unlike most alcoholic menstrua, is virtually painless.

Efficiency of Action—Digitaline Nativelle is pure digitoxin. It is rapidly, completely and uniformly absorbed—neither too fast nor too slow—providing a steady and predictable action upon the heart muscle.

Dependability of Performance—Digitaline Nativelle [digitoxin] is the pure active glycoside insuring optimum range of cardiotonic activity. Digitoxin is a drug of choice when a purified digitalis product is desired.

Adequate Margin of Safety—Digitaline Nativelle provides virtual freedom from annoying local side effects which may occur with the galenicals, and its margin of safety is unexcelled by any other purified preparation. A product of Nativelle, Inc.

E. Fougera & Co., Inc.

FOUGERA

Hicksville, Long Island, N. Y.

ANNOUNCING SCHERING'S NEW MYOGESIC[X]

RELA™ **EASES STRAINS SPRAINS & LOW BACK PAINS...!**

CARISOPRODOL

RELA—a new myogesic for better relaxant *and* analgesic therapy—more adept management of spasm and pain in strains, sprains and low back pains.

RELA—though a single drug—is a true myogesic and works rapidly to achieve three desired effects...

Rela relaxes acute muscle spasm
Relief of muscle spasm (96% excellent to good effectiveness)[1]

Rela provides a unique quality of persistent pain relief through its relaxant and analgesic actions
"Relief from pain was usually rapid and sometimes dramatic"[1]

Rela, through relaxation and analgesia, assures daytime ease and nighttime rest
"... A number of patients reported freedom from insomnia which they attributed to freedom from pain."[1]

indications: RELA is most beneficial in those conditions of the musculoskeletal system manifesting pain, stiffness and spasm.

safety: Studies of more than 1400 patients indicate that the toxicity of RELA is exceptionally low. In human subjects, respiratory, blood pressure or blood chemistry changes and/or renal, hepatic or endocrine dysfunction have not been reported.

dosage: The usual adult dosage of RELA is one tablet 3 times daily and at bedtime. RELA has a rapid onset of action, with relief usually apparent within 30 minutes, and persisting for at least 6 hours.

supply: RELA is available as 350 mg., pink, coated tablets in bottles of 30.

1. Kuge, T.: To be published. H-227

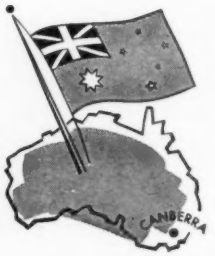
MYOGESIC
muscle-analgesic relaxant

Schering

Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA



Surgical treatment of aortic stenosis—In the *Medical Journal of Australia*, Drs. Douglas Stuckey, R. G. Epps and Ian Monk from the Cardiac Investigation Clinic, Royal North Shore Hospital, Sydney, reported briefly on their experience in the surgical treatment of 21 patients with aortic stenosis. The ages of these patients, who were treated by aortic valvotomy, ranged from 13 to 75 years, (all except four were 40 to 60 years old). Sixteen were men and five were women; a history of rheumatic fever was elicited in only five cases.

The authors stressed the two symptoms which are specifically related to obstruction of the circulation: angina pectoris and effort syncope. Thirteen patients exhibited angina pectoris of the classic type on exertion, and it was usually a disabling symptom. Eight patients had effort syncope, which is probably the result of restricted cardiac output. Because aortic stenosis can be easily overlooked on physical examination, suspicion should be aroused by symptoms or signs of left ventricular stress without obvious cause, or by a patient with a systolic murmur and normal blood pressure who has angina on effort.

Electrocardiographic abnormalities were noted in all cases in this series, with left bundle-branch block in one and varying degrees of anormal left ventricular preponderance in the other cases. Of importance is the fact that normal x-ray findings are consistent with the presence of severe aortic stenosis causing disabling symptoms. Of 16 patients with aortic stenosis who were examined by tomography, only one failed to show calcium deposits in the valve area.

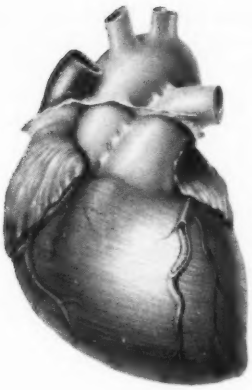
Percutaneous puncture of the left ventricle from the region of the cardiac apex was performed under local anesthesia after premedication in 19 patients in this series. Pressures recorded within the left ventricular cavity were compared with those obtained from a branchial artery. This investigation is now regarded as an essential part of the assessment for operation.

Open aortic valvotomy was performed on the three youngest patients, 13, 14 and 24 years old, by the transaortic route with occlusion of the circulation under hypothermia. Closed aortic valvotomy, based on Brock's technic, was performed by the transventricular method on all the other patients with varying degrees of valvular calcification. The results obtained after operation were as follows: excellent, three; good, 11 (one death three months after operation); fair, three (one death a year after operation), and poor, one (the patient died three months postoperatively). There were three operative deaths in this series.

AUSTRIA

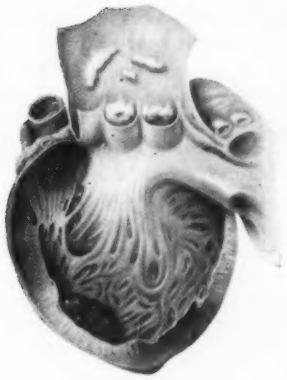
Gaucher's disease in childhood—At a meeting of the Society of Physicians in Vienna, Drs. Rosenkranz and Swoboda presented the clinical characteristics of this rare storage disease on the basis of four cases observed during the last 10 years at the Pediatric

(Continued on page A-100)



IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

. . . the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

. . . it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

Protects your coronary patient better than vasodilation alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important – Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition...and his operative arteries are dilated to enhance myocardial blood supply.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J. E. F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Miltrate

Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *New Brunswick, N.J.*

CWL-1388

®TRADE-MARK

Clinic of the University of Vienna. Two sisters showed only the symptom of frequent attacks of epistaxis, and the splenic tumor in each case regressed during the second decade of life. The third child had cirrhosis of the liver, which is extremely rare in this disease. The fourth patient, who died prematurely, showed signs of an acute, early form of Gaucher's disease complicated by neurologic focal symptoms.

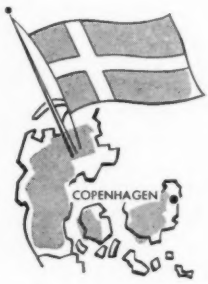
Dr. Seitelberger discussed the histopathology of this disease, and defined it as a sphingolipoid thesaurismosis (storage disease) which attacks the reticuloendothelial system. The histochemical and biochemical findings show that the largest portion of storage material is a glucocerebroside which, in a bound form cellularly, is present as lipoprotein of certain submicroscopic structures. Another material present is an easily soluble acid glucolipid. In contrast to other types of sphingolipoidosis, the cerebral parenchyma is not primarily affected by the pathologic process in Gaucher's disease, particularly in its infantile neural form.

Dr. Rieder stated that data on cases of Gaucher's disease are available, and that some of these cases include entire families. In adults, pancytopenia is the first symptom; thrombopenia occasionally will lead to hemorrhagic diathesis. The diagnosis frequently can be made from the simple concentration of leukocytes, as typical Gaucher cells are manifest in the smears. In biopsy of the bone marrow, extensive fibrotic spots in the marrow, within which Gaucher cells can be recognized, may be observed in addition to the medullary tissue rich in cells. The disease often progresses to severe destruction of the bone, similar to that seen in plasmocytomas.

Sequelae of head injuries—At the same meeting, Dr. Holub reported on 2,035 patients with sequelae of cranial and brain injuries who were observed at the First Traumatological Station. He discussed this subject from the point of view of surgery, with special emphasis on objective findings and treatment. The report also included 1,157 patients who were continuously treated at the neurosurgical station of the First Surgical Clinic of the University of Vienna. In the majority of these cases, the so-called post-traumatic syndrome was primarily an organic disease, but psychic influences must be considered also. In addition, the lecturer mentioned the possibility of making an objective diagnosis, the treatment, and the prevention of the post-traumatic syndrome.

Dr. Gerstenbrand stated that brain contusion is not necessarily associated with a typical syndrome of concussion; therefore, unconsciousness and other symptoms of concussion sometimes are not markedly expressed in such cases. In instances of anteroposterior trauma, an accurate neurologic examination will reveal distinctly recognizable frontal signs. Such patients, in contrast to those with a simple brain concussion, exhibit a state of confusion which may last for days, striking sluggishness, and headaches of longer duration. One should watch for these symptoms, because many cranially injured patients receive the effect of the force in the frontal area.

DENMARK



Encephalitis—Ejner Pedersen and Carsten Rindom Schiøtt have described five cases of subacute encephalitis. In two of these, biopsy specimens revealed intranuclear inclusion bodies, and in two others, inclusion bodies were noted at autopsy. Only in one case was the diagnosis made on the basis of clinical observations.

The clinical pictures and laboratory findings were so uniform that Schiøtt and Pedersen found it necessary to give a detailed description of only one case, although the histologic findings in biopsy and autopsy material from all five cases were reported.

The etiology of the disease is unknown, but it is reasonable to assume that the causative agent is a virus. The finding of inclusion bodies is significant in supporting this view.

It has been suggested that the designation "subacute inclusion encephalitis" for this disease should be discarded, partly because of the occurrence of inclusion bodies and partly because the diagnosis may be made only on the basis of the clinical course and laboratory findings, especially those shown by electroencephalography.

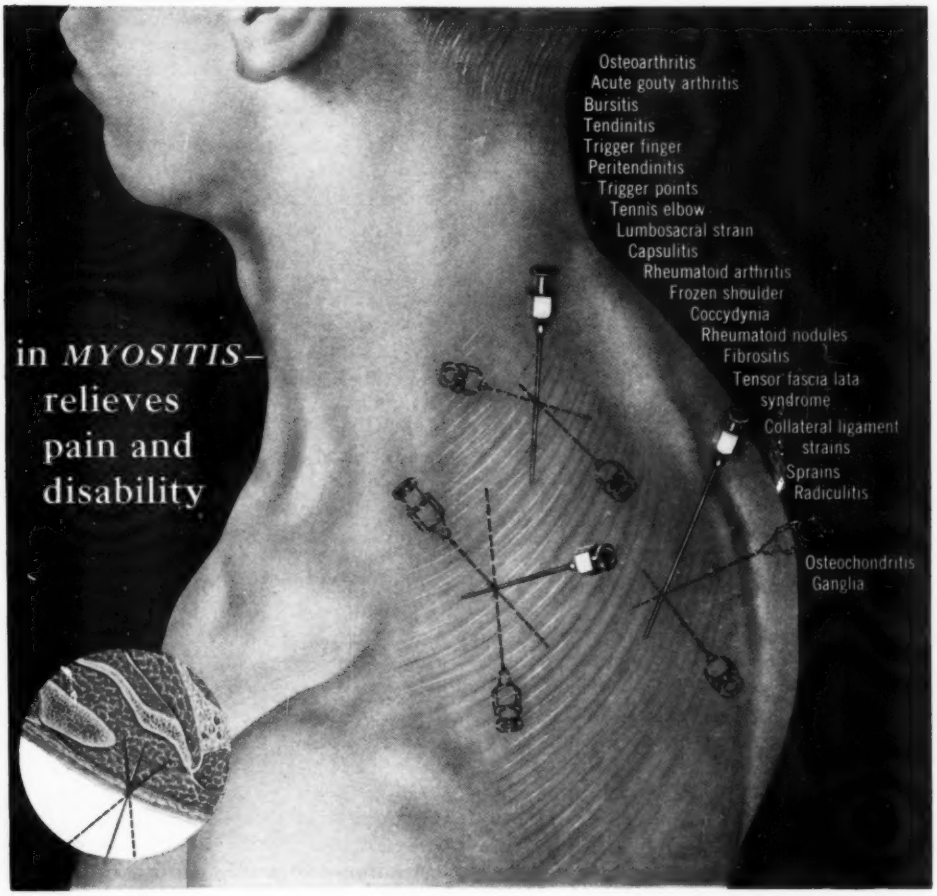
Asian influenza—Twelve cases of so-called Asian influenza were reported by Bent de Fine Olivarius and Mogens Fog in the *Danish Medical Bulletin*. In one case the nervous symptoms were interpreted as resulting from a toxic encephalopathy and not as an encephalitis proper. In the

(Continued on page A-102)

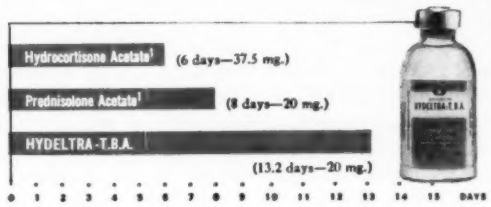
HYDELTRA®-T.B.A.

(Prednisolone tertiary-butylacetate, Merck)

for relief that lasts—longer



Anti-inflammatory effect lasts longer than that provided by any other steroid ester


Hydrocortisone Acetate[1]
(6 days—37.5 mg.)
Prednisolone Acetate[1]
(8 days—20 mg.)
HYDELTRA-T.B.A.
(13.2 days—20 mg.)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 DAYS

Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone *tertiary*-butylacetate, in 5-cc. vials.

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA

remaining cases, the signs and symptoms suggested an encephalitis, and the close relation in time between the occurrence of the influenza and the cerebral symptoms indicated that an influenza virus of the Asian strain was the causative agent, although final serologic proof or isolation of the virus was lacking.

While the prognosis for the patients with cerebral symptoms was good, it was more uncertain in patients with epileptic seizures. The presumed predominant corticocerebral damage in these cases is probably irreparable. In one patient the epileptic seizures continued in spite of intensive antiepileptic treatment; in the others no seizures were seen during the observation period, but too short a time has elapsed to permit any final evaluation of the prognosis.

However, it is not possible to take the relatively great number of patients with encephalitis seen over a short period of time as an expression of a special neurotropism of the Asian strain of influenza. The purpose of reporting these cases has been to point out that probably neuroinfections have been rather common during the Asian influenza epidemic and that the possibility of sequelae to neuroinfections with Asian influenza virus should be borne in mind when clinical neurologic pictures otherwise unexplained are encountered in the future.

Nitrous oxide treatment in chronic granulocytic leukemia—The following effects were observed by H. C. A. Lassen and H. Sund Kristensen after the prolonged inhalation of nitrous oxide by two patients with chronic granulocytic leukemia:

1. The total number of myeloid white cells and thrombocytes decreased considerably after 5 to 15 days of treatment, but then rose rapidly a few days after withdrawal of the anesthetic.

2. The erythrocytes and the hemoglobin content were not affected.

3. Granulopoiesis changed in such a way as to resemble the bone-marrow picture seen in pernicious anemia.

4. It has been known for some time that the vitamin B_{12} content in the blood of patients with chronic granulocytic leukemia is considerably above normal. The cause of this is not clear, but Mollin and associates in 1956 found that patients with chronic granulocytic leukemia retained vitamin B_{12} far in excess of the normal amount. Mendelsohn and co-workers in 1958 showed this to be due to an increased content of a B_{12}-binding protein in the a_1 fraction of the serum globulin. During the nitrous oxide treatment a sharp fall in the B_{12} content was observed, although normal values were not reached. This fall was followed by a rapid increase after discontinuation of the anesthetic.

5. During the four courses of treatment, certain changes in the patients' mental state were noticed. In the beginning they felt as if they were inebriated, but later they complained of mental depression and extreme lassitude. On two occasions even stupor or coma ensued.

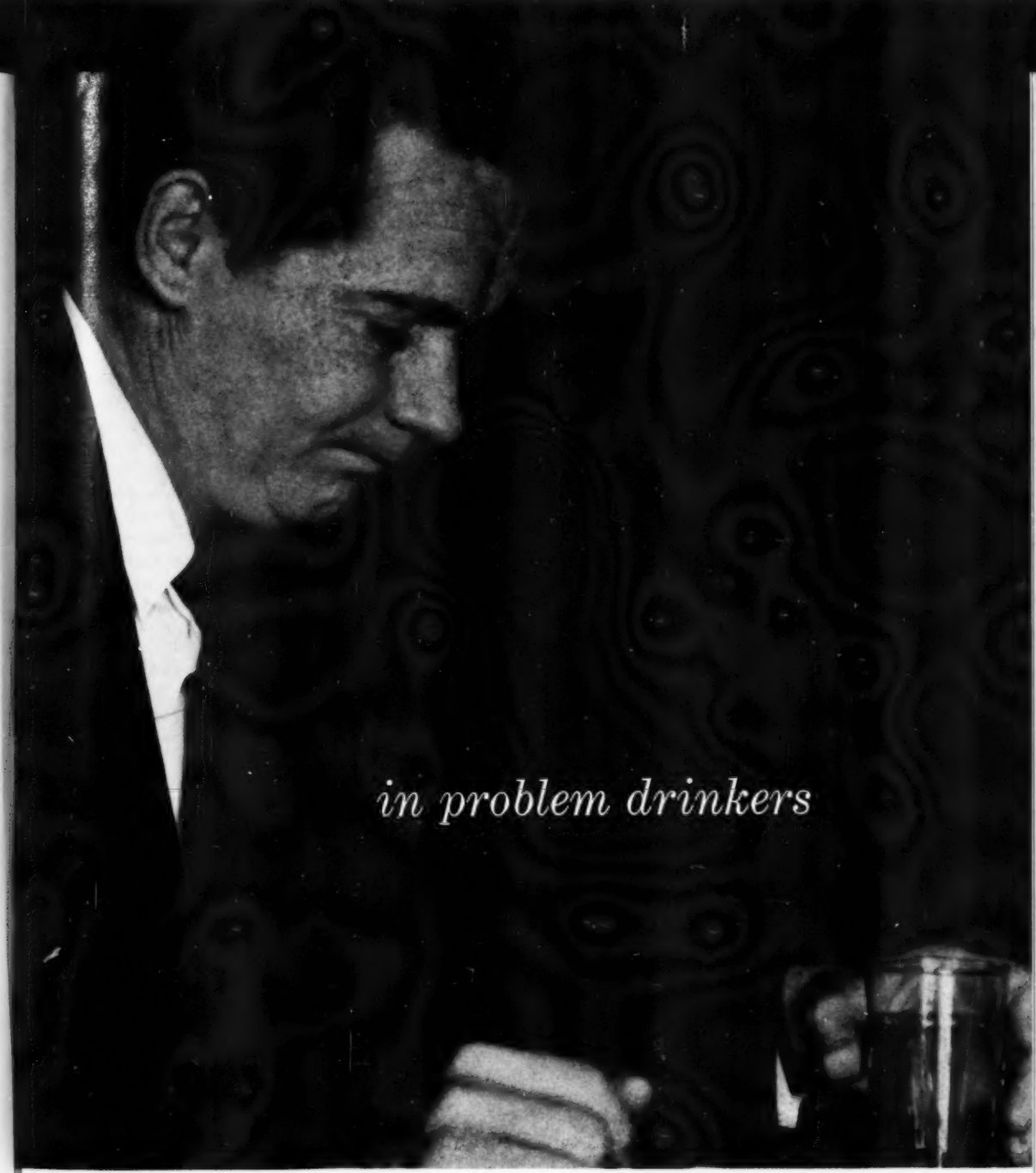
The authors of this study concluded that prolonged inhalation of nitrous oxide is not to be recommended as a therapeutic agent in cases of chronic granulocytic leukemia. However, from a theoretical point of view these cases are of interest because they stress the fact that nitrous oxide has a marked cytotoxic effect on the bone marrow when used over prolonged periods.

ENGLAND

A good year for health—According to the Ministry of Health's annual review of the nation's health 1959 was a good year, especially in the decline of poliomyelitis, which was easily the greatest in several years. There were only 86 deaths from poliomyelitis, against 147 in 1958 and 246 in 1957, but how far this improved position was the result of the rising level of antipoliomyelitis vaccination will always be impossible to estimate. Gradually the degree of protection of the younger groups of the population was extended, and by Christmas more than nine million (about 74 per cent) of those in the most susceptible age group, i.e., up to 16 years of age, had received two or more injections of vaccine.

An increase in the number of cases of diphtheria from 182 in 1958 and 192 in 1957 to 271 in 1959 reinforced a recent warning concerning the importance of a continued high level of diphtheria immunization in spite of the present low mortality from the disease. While the percentage of primary immunizations in children less than five years of age was rising slightly, the acceptance rate for booster doses before and during the school years had fallen. It seems clear that there

(Continued on page A-104)



Vistaril®

hydroxyzine pamoate

dispels tension...
maintains tranquility

When tension and anxiety "drive him to drink," the problem drinker often finds that VISTARIL, by maintaining tranquility, restores perspective and helps him accept counsel more readily.

VISTARIL has demonstrated a wide margin of safety even in large doses (300-400 mg. daily) over prolonged periods. Clinical studies of alcoholism have shown that VISTARIL produces no significant depression of blood pressure, pulse rate, or respiration in chronic drinkers.

Capsules—25, 50, and 100 mg. *Parenteral Solution* (as the HCl)—25 mg. per cc., 10 cc. vials and 2 cc. Steraject® Cartridges; 50 mg. per cc., 2 cc. ampules.

Professional literature available on request from the Medical Department, Pfizer Laboratories, Div., Chas. Pfizer & Co., Inc., Brooklyn 6, New York

Pfizer *Science for the world's well-being™*

is still a danger that this disease could again become a serious problem and that efforts to maintain a high level of immunization of children cannot be relaxed.

The customary biennial rhythm of measles was repeated, the total number of reported cases rising to well over half a million. There was also an increase in cases of scarlet fever during the year. 45,705 as compared with 36,387 in 1958 and 28,447 in 1957.

For the second consecutive winter, influenza was prevalent early in the year. It began toward the end of January and reached its peak a month later. In England and Wales deaths from this cause totaled 7,850, against 2,611 and 6,333 in 1958 and 1957, respectively. More deaths from pneumonia (30,767) and bronchitis (27,716) were recorded, the great majority occurring during the first quarter of the year.

Treatment of hemangioma in children—There was an interesting discussion on this subject in the section of dermatology at the Royal Society of Medicine when Dr. Brian Russell showed two cases of hemangioma in children, in each of whom the hemangioma had eventually disappeared without any treatment, leaving only a small fleshy swelling.

Dr. F. F. Hellier said that he felt unhappy about these cases. The hemangiomas probably disappear in time, but it is a terrible handicap for a child to have a severe blemish on his face or on some other visible part until he is five or seven years old. "We know," he added, "what children are. When they see another child with a blemish, they say, 'Don't go near that little girl; she has a mark on her face.' Psychiatrists tell us that such things happening in childhood may have serious effects in later life. I have seen little children with such blemishes walking about trying to hide the affected part of the face. We have no right to let children with exposed birthmarks go through seven years of life suffering what is really psychologic trauma. Any conspicuous lesion should be treated." Dr. Hellier treats strawberry marks and other such blemishes on exposed areas because he feels it is fair to both the child and mother.

Dr. R. T. Brain supported Dr. Hellier. When these marks are obvious his practice is to give x-ray treatments in doses of 250 to 300 r at monthly intervals; the total dosage practically never exceeds 1000 r. Atrophy does not result from this treatment, although it does occur in the case of large lesions whether they are treated or not. There is redundant, pale, wrinkled skin which needs trimming, and that is a matter of simple excision. In a series of 614 cases reported by Drs. Brain and Calnan in 1952, 147 lesions were untreated and they cleared up nearly as well as the treated lesions, although not so quickly. Dr. Brain treats the blemishes if they are exposed, but not if they are on the scalp.

Dr. G. B. Mitchell-Heggs said that in these cases the desperate mother takes her child from one hospital to another until she finds someone who will take action. In addition to this type of case, he feels that any child whose vision is impaired or whose feeding or excretion is handicapped should be watched. The distressed parents wonder whether their child is being properly fed or whether the ulcers, which soon appear in the napkin region, will heal, and they travel in search of positive action. After a period of observation, if there is any increase in size of the lesion or if there is no regression, he usually recommends appropriate radiotherapy and, in certain cases, surgery.

Dr. B. Bentley Phillips has been treating these nevi for a number of years with thorium X paint, administering a total of about 18 paintings. Whether it does a great amount of good he could not say. He believes that it obviates the trouble mentioned by Dr. Mitchell-Heggs in that it stops the parents taking the patient from one hospital to another. If no treatment is given, the parents will continue to take the child around until they find someone enthusiastic enough to treat him.

Dr. Russell agreed with Dr. Mitchell-Heggs' view that if the hemangioma is likely to interfere with breathing, feeding, vision or defecation, something should be done; otherwise not. He had never seen a child under school age who showed any serious emotional disturbance because of a simple hemangioma. It was the mother who was anxious.

Treatment of motion sickness—In opening a recent discussion at the Royal Society of Medicine on the prevention and treatment of motion sickness, Dr. E. M. Glaser of London, a research physiologist, said that, like all reflexes, motion sickness may be modified by impulses from the cerebral hemispheres. The most important are the inhibition of motion sickness by interest in other things, the enhancement of motion sickness by interest in one's symptoms or by anxiety, and the diminution of motion sickness by habituation to wave motion. It follows that

(Continued on page A-106)

Just two tablets *at bedtime*

RAUWILOID®

alseroxylon, 2 mg.

...does more than lower blood pressure!

Seven years of experience show that RAUWILOID also affords

Safety based on negligible incidence of side actions

Freedom from concern over sudden hypotensive episodes or unwanted biochemical alterations

Practicality.. simplicity of dosage .. applicable to a wide range of patients

When more potent drugs are needed, prescribe one of the *convenient single-tablet combinations*

Rauwiloid® + Veriloid®
alseroxylon 1 mg. and alkavervir 3 mg.

or

Rauwiloid® + Hexamethonium
alseroxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.

Riker

Northridge, California

some lessening of motion sickness can be achieved by lying down (when vestibular stimulation is the least), by interesting activities, and by habituation to the motion. Since habituation is more rapid when the head is held up, it seems best to lie down until treatment by drugs has taken effect, and then to get up to allow habituation.

For severe motion at sea or in the air and during exposures lasting not more than a few hours, single doses of 0.6 to 1.2 mg. hyoscine hydrobromide have invariably been found significantly more effective than any other drug available at present. Such single doses are also accompanied by fewer side effects than is treatment with any other drug and by little or no impairment of efficiency; but, in the absence of wave motion, hyoscine can give rise to more side effects than do other drugs.

Among proprietary remedies, promethazine (PHENERGAN® or Avomine) has been effective in single doses and, to some extent, cyclizine hydrochloride (MAREZINE®), diphenhydramine hydrochloride (BENADRYL® hydrochloride), and dimenhydrinate (DRAMAMINE®) are also effective.

When the motion is mild, as on large liners, the advantages of hyoscine over other drugs may be less obvious than it is in the presence of sharp motion. American experiments on troopships were so designed that only long-acting drugs could have any effect; and in these experiments a dose of 50 mg. meclizine hydrochloride (Ancolan, BONINE®, Sealegs or Postafene), which has a very long action, was found best, followed by promethazine and cyclizine hydrochloride, which are also long-acting drugs.

FINLAND

Health of executives—In *Duodecim*, L. Noro, S. G. Jokipii and P. Sumari have published the results of a study of the health of 350 executives. The investigation included a fairly thorough medical examination supplemented, when necessary, by examination by specialists.

The subjects studied were all healthy working people. Ninety-five per cent said they liked their work, but 33 per cent said that they either did not feel on top of the job or were not masters of their own time; 25 per cent complained of the lack of efficient fellow workers or of a competent successor. Forty-three per cent of the group did not smoke and 6 per cent were teetotalers. Various medicines were taken regularly by 34 per cent. Thirty-eight per cent traveled chiefly by automobile, but only 10 per cent avoided walking and other outdoor activities.

Thirty-three per cent of the subjects were more than 10 per cent overweight. The most common other findings were: increased cholesterol level, 44 per cent; electrocardiographic changes, 31.6 per cent; diminished heart functions on exercising, 20 per cent; increased diastolic blood pressure, 19 per cent; roentgenographic changes in the lungs, 17.4 per cent; roentgenographic changes in the heart, 14.1 per cent; eczemas, 12 per cent; lesions of the ear, 11 per cent; increased sedimentation rate, 11 per cent; hemorrhoids, 6 per cent; varicose veins, 5 per cent; prostatic changes, 3 per cent; albuminuria, 2 per cent; diabetes, 1 per cent. In addition, 34 per cent had reduced short-range vision, and 14 per cent had reduced long-range vision; 14 per cent had strabismus and 25 per cent had heterophoria. None of the group had cancer.

The authors of this study believe that regular and thorough health examinations may reveal at an early stage a number of diseases and defects amenable to treatment; in certain cases, they also may help those examined to overcome needless fears and anxieties regarding their health. Furthermore, such examinations offer an excellent opportunity for individual health education. The authors recommended that industrial and commercial firms provide for such examinations for executive personnel.

FRANCE

Kidney graft—In 1953, Dr. J. Hamburger and Dr. Servelle attempted the first kidney graft in France. The kidney was taken from the mother of the recipient. After 20 days of functioning well, the organ was suddenly stricken by massive apoplectic lesions, and in a few hours it ceased to work. Later, Merril of Boston showed that the disease which destroys such grafts results from the presence of old, chronic renal lesions. In 1959, Dr. Merril performed a successful kidney graft; notwithstanding a postoperative pyelonephritis, the patient survived for eight months.

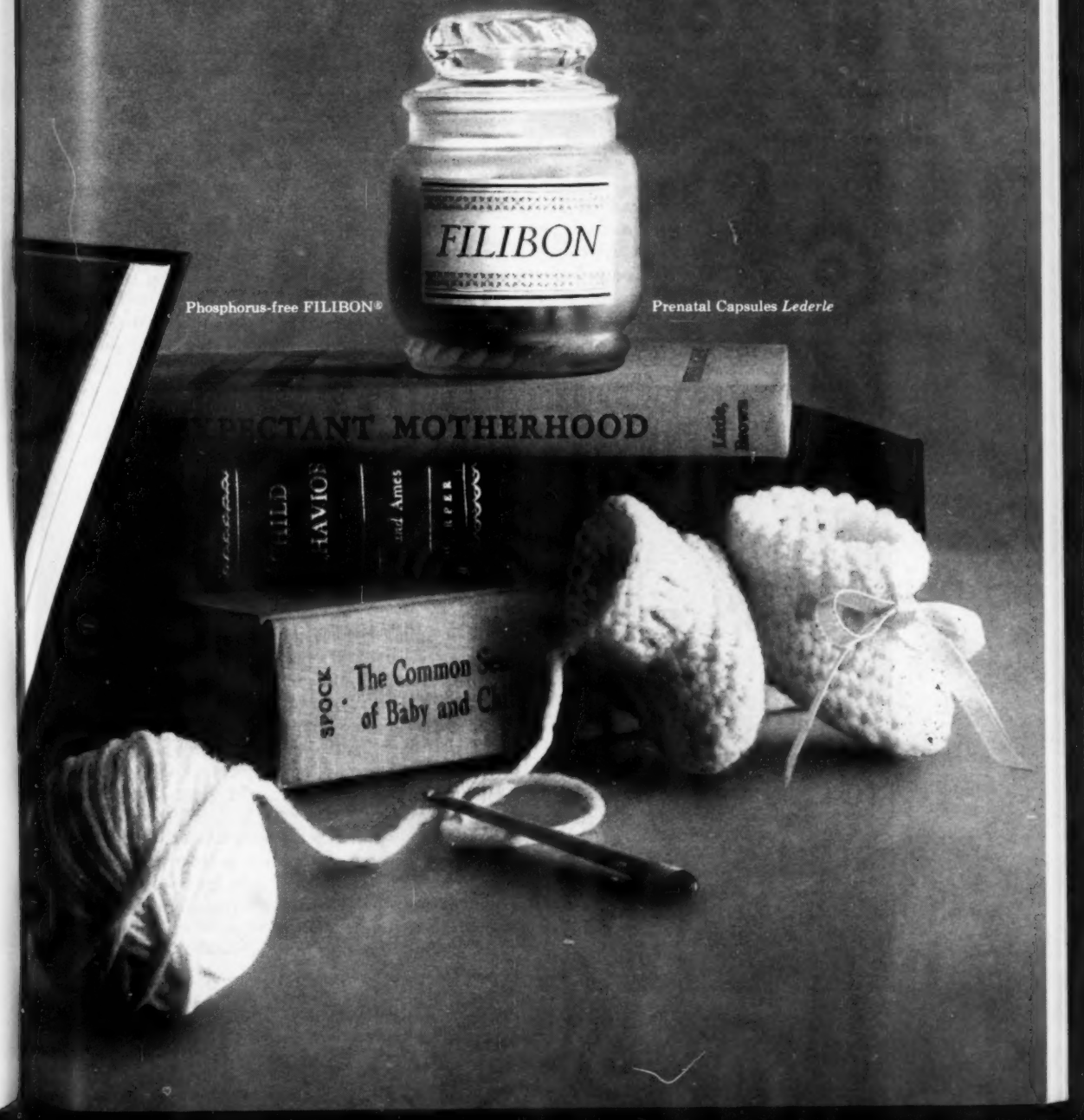
Dr. Hamburger has reported a kidney graft

(Continued on page A-108)

AN IMPORTANT PART OF THE PRENATAL PLAN...

the decorative FILIBON jar, an objective reminder of the single capsule daily dose...assuring effective nutritional support every day with the complete FILIBON formula. Includes a well-tolerated iron hematinic, noninhibitory intrinsic factor in readily accepted small, oil-free capsules. For complete formula see Physicians' Desk Reference, 1960, page 697.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.



which has been successful for four months. The patient is a 37 year old man who had had albuminuria since 1951. He also had had progressive nephritis, complicated by retinitis. In May 1959, the nonprotein nitrogen in his blood reached 3 gm.; the urea clearance test and the examination of the other renal functions showed a functional breakdown which was so marked that the patient was not expected to survive for more than a few months. The cause of this glomerulonephritis was unknown.

The donor of the kidney was the patient's brother, a heterozygous twin, who resembled him very much but had certain apparent differences. Exploration of their blood groups showed 15 common characteristics and three differences. The leukocytic antigens were the same, except that one of them was present in the recipient and absent in the donor. The functional integrity of the two kidneys also was checked.

The transplantation was performed on June 29, 1959. On June 22, the patient received general irradiation with 260 rads radioactive cobalt: he received 200 rads on June 28. The radiation was directed at the entire body homogeneously.

Dr. J. Vaysse removed the kidney of the donor, using hypothermia at 29° C. Heparin was injected through an arterial orifice. The kidney was then set in place in the recipient's right iliac fossa; the artery was anastomosed to the hypogastric artery, the vein to the external iliac vein, and the ureter was attached to the fundus of the bladder. The duration of the operation was four and a half hours. After the operation, the patient was isolated and strictly protected against any septic contact.

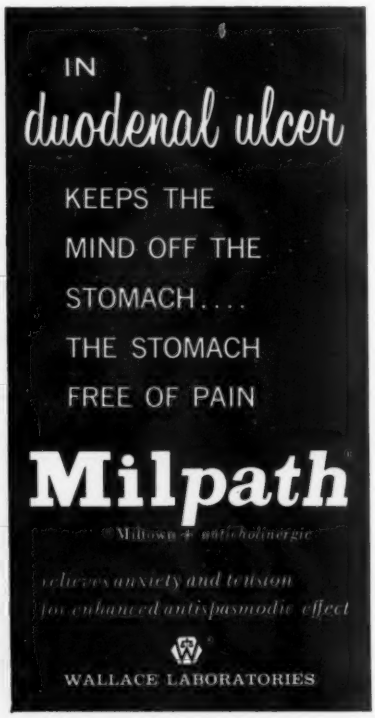
In subsequent weeks blood aplasia occurred due to the massive irradiation the patient had received. The granulocytes dropped to 50 per mm^3. On the fifteenth postoperative day a little purpura developed on the patient's trunk, but there was no bleeding. The granulocytes recovered on the twenty-third day after the operation. The patient ran a fever as high as 40° C. from the start of the second postoperative day until the ninth. A second temperature rise occurred on the fifteenth day, but the temperature dropped when the granulocytes reappeared.

On the whole, the kidney functioned normally, excreting up to 1800 cc. of urine on the third postoperative day. The uremia decreased from 3 gm. to 0.32 gm. The albuminuria was reduced to 0.2 mg. per minute; the urea clearance was 45 ml. per minute. Suddenly, on the fifteenth postoperative day, a kidney disease developed with significant albuminuria, a drop in the urea clearance to 6 ml. per minute, and uremia up to 1.25 gm. This disease lasted for eight days. After this, the albuminuria disappeared and the elimination became normal.

On the seventy-third postoperative day, the blood urea was normal at 0.35 gm. and results of intravenous urography also were normal. The eye fundus was almost normal, and the arterial tension was steady at 90 to 140 mm. It had been recorded from 110 to 190 mm. Hg. This condition continued more than 100 days after the operation.

The success of this graft seemed to result from a combination of the following conditions: (1) the existence of a chronic nephritis in the recipient patient; (2) the ties of consanguinity between the donor and the recipient who, although not homozygous twins, showed great similarity in their antigenic reactions; and (3) the aid of radiotherapy. The chronic nephritic factor, which Merril considered extremely important, was demonstrated by a graft of a skin fragment which sloughed off on the twenty-first postoperative day.

Dr. Hamburger and co-workers reported on this operation in *La Presse médicale*.



Postgraduate
Medicine

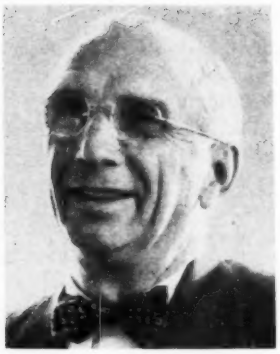
Special Issue
MARCH 1960

Evaluation of Early Diagnosis of Cancer

Annual Scientific Session

American Cancer Society

October 1959, New York



HAROLD S. DIEHL

Introduction

THIS special issue of POSTGRADUATE MEDICINE contains the papers presented at the Symposium on Evaluation of Early Diagnosis of Cancer, the subject of the American Cancer Society's Annual Scientific Session, held in New York on October 26 and 27, 1959. The Society is grateful to the publishers and the editorial staff of this journal for their concerted efforts in expediting the publication of this material.

Until the day when practical and effective preventive measures against cancer become available, the most hopeful methods of cancer control are early diagnosis and prompt, adequate treatment. It is toward this end that the American Cancer Society has been striving in its education and service programs from its inception in 1913. Since 1945, the Society has also been devoting a major portion of its resources and efforts to the support of research on the etiology, pathogenesis, therapy and prevention of cancer.

In accord with its policy of continuing critical appraisal of its programs, the Society, in conjunction with its annual meeting, holds each year a scientific conference which brings together clinicians and investigators for discussion and evaluation of the progress made. The material in this issue presents current concepts as put forth by the group of specialists in the cancer field who assembled to deliberate the important aspects of early diagnosis.

It is hoped that this critical review and evaluation of our knowledge concerning the manifestations of early cancer and their management will give physicians everywhere renewed stimulus in the approach to the problem in their own practice and encourage more effective use of the presently available methods of early detection and diagnosis. The doctor who makes the early diagnosis and provides for adequate treatment, thus helping to prolong a human life, should, indeed, experience great satisfaction.

HAROLD S. DIEHL, M.D.
Senior Vice-president for Research and Medical Affairs and Deputy Executive Vice-president, American Cancer Society

Scientific Session of the American Cancer Society

PURPOSE OF THE SYMPOSIUM

EUGENE P. PENDERGRASS*

University of Pennsylvania School of Medicine, Philadelphia

EUGENE P. PENDERGRASS

ONE of the great achievements of the American Cancer Society over the years has been the awakening of the public to the recognition and acceptance of its responsibility in the detection of cancer. This has been brought about through education of laymen concerning signs and symptoms of the disease and encouragement of periodic physical examinations. This measure has been demonstrably lessening the delay in diagnosis which the patient to a large extent controls.

It is also essential that the medical profession be more alert to the diagnosis of cancer and more efficient in its detection. Slow progress in the past is, perhaps, not surprising when it is realized that we are confronted with a disease that has no characteristic signs or symptoms and too often is observed for a period of time until recognition becomes possible or a presumptive diagnosis is made. Since public education in cancer will continue to bring to physicians an increasing load of patients with lesions not easily definable, the necessity of determining the nature of these lesions at the earliest possible moment becomes an acute one which must be served if we are to contribute adequately to improved cancer control.

In planning this symposium on the "Evaluation of early diagnosis of cancer," there immediately come to mind four considerations with which we must concern ourselves.

The first and most practical one is "The economics of cancer detection." Under this heading we will consider such factors as personnel, facilities and methods of examination as they relate to the accomplishment of early detection. We probably cannot hope to agree on the answer to the basic question, "What is early cancer?", but we can arrive at a better understanding of the early diagnosis of cancer if we spend some time on its interpretation. More tangible items, on which we can be

*President, American Cancer Society; Professor of Radiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

more unanimous in agreement, are those dealing with what constitutes an adequate cancer checkup and what the changing responsibilities of the physician are in cancer control.

The logical second consideration, "The value of periodic examinations in cancer detection," gives us opportunity to consider cancer from the viewpoint of the various sites in which it appears and to get the opinions of a panel on the question "Does periodic examination of well persons increase longevity?" In the answer to this question lies the justification of our constant surveillance of well persons for early signs of cancer.

The third consideration, a controversial subject, is "Precancerous lesions and their treatment." On this we will hear the opinions of physicians in the various disciplines and specialties from whose experience we will get valuable information.

Finally, the fourth consideration, the large subject of "Treatment of early cancer," will give us a general picture of the latest results of application of the best available therapeutic methods to cancers of the various sites.

This conference should present material of interest and practical use for all of us. We should not get bogged down in the semantics of early cancer. In my opinion there are many lesions that are early localized cancers. There are others that, although very small, have extended beyond the original focus. From the discussions here in these two days we will hope to obtain the stimulus and the guidance to help us increase our acuity and effectiveness in the early diagnosis of cancer.

MEETINGS *and Postgraduate Courses*

AMERICAN COLLEGE OF SURGEONS, SAN FRANCISCO: The date of the 1960 Clinical Congress has been changed to October 10-14. For further information, write to: Dr. William E. Adams, Secretary, American College of Surgeons, 40 East Erie Street, Chicago 11.

AMERICAN COLLEGE OF SURGEONS: Sectional meeting to be held at Hotel Leamington in Minneapolis April 11-13 and at the Mayo Clinic, Rochester, Minnesota, April 14. For further information, write to: Dr. H. P. Saunders, Associate Director, American College of Surgeons, 40 East Erie Street, Chicago 11.

BIOLOGICAL PHOTOGRAPHIC ASSOCIATION, MILWAUKEE: Second Midwestern regional meeting, April 1-3, at St. Francis Hospital. Papers, movies or exhibit prints for the program may be submitted to Mr. Lou Facto, Program Chairman, Morrill Hall, Iowa State University, Ames. For further information, write to: Mr. Charles Deutsch, Veterans Administration Hospital, Iowa City.

CHILDREN'S HOSPITAL OF PHILADELPHIA AND GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA: Refresher courses:

Pediatric advances, May 30-June 3

Practical pediatric hematology, June 6-10

For further information, write to: Dr. Irving J. Wolman, Director of Post-Graduate Education, The Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia 46.

MAYO CLINIC AND MAYO FOUNDATION, ROCHESTER, MINNESOTA: Clinical reviews, April 4-6. For further information, write to: M. G. Brataas, Mayo Clinic, Rochester, Minn.

PAN-PACIFIC SURGICAL ASSOCIATION, HONOLULU: Eighth congress, September 27-October 5. For further information, write to: Dr. F. J. Pinkerton, Director General, Pan-Pacific Surgical Association, Suite 230, Alexander Young Building, Honolulu 13, Hawaii.

What Is Early Cancer?

DANELY P. SLAUGHTER*

University of Illinois College of Medicine, Chicago

DANELY P. SLAUGHTER

THE answer to the question of the title today is a much more complicated concept than it was 10 or 15 years ago when the reply would have been in terms of size and duration of the primary lesion plus extent of secondary spread. The connotations of the question really refer to the relative curability of a given malignant tumor, or at least to the possibilities of long-term control, with the patient continuing as a functional unit in reasonably good health. Additional implications of the query require consideration of carcinoma *in situ*, or preinvasive cancer, and even of the antecedent so-called precancerous changes. This way of thinking can be carried back further in the evolution of a malignant neoplastic process to a study of the background conditions which eventuate in an irreversible cellular change leading inevitably to the autonomous and invasive reproduction of cells.

Enough new factual knowledge has accumulated to form a pattern which, haphazard as it may be, allows changes in our philosophic attitudes toward cancer. Macdonald's catch phrase "biologic predeterminism" was one of the first indications of such a shift in point of view and has served both a useful and a harmful function, the latter resulting from shallow thinking which used the concept as an excuse for inadequate therapy. Aside from the possible origin of this phrase from the teachings of John Knox, we, as objective scientists, must search out the background reasons for the modicum of truth expressed.

In spite of the observed individual vagaries of the natural history of certain tumors within various classes of neoplasms, in general it is still a truism that the sooner a cancer is identified in its natural evolution, the greater is the likelihood of successful treatment. No one can reasonably argue that a 1 cm. superficial carcinoma of the lateral border of the tongue is no more curable at that stage than the same tumor allowed to progress for six months or a year to a stage of deep muscular invasion,

*Clinical Professor of Surgery and Director of Tumor Clinic, University of Illinois College of Medicine, Chicago, Illinois.

when it is 4 to 5 cm. in size and has multiple node metastases. The same is true of cancer of the uterine cervix, rectum, stomach and so forth, ad infinitum. In other words, if a cancer is apprehended in the tort stage rather than in the stage of a biologic felony, the revolt against the cellular community is more easily contained.

Conversely, it is equally true that no two cancers of the tongue, 1 cm. in size, are curable at the same level of effort in different individuals. The variations in this factor of size in relation to curability are even more apparent in tumors arising in tissues under separate endocrine regulation, such as mammary carcinoma in particular. The size of a primary breast cancer has relation to its curability only within very broad limits, but even for purposes of theoretical generalization there must be more precise definition of terms. Microscopic identification is one important factor: in general, a papillary breast carcinoma of 5 to 6 cm. is more curable than an undifferentiated ductal carcinoma 2 cm. in diameter. In this sense a papillary tumor larger than a lesion of the "carcinoma simplex" type is an earlier cancer. Other factors, some suspected and many not yet known, modify the course of breast cancer. The menopausal status or related physiologic steroid milieu may play a part in curability or long-term survival.

The vague and as yet only hypothetical factor of "host resistance," or the lack thereof, undoubtedly plays an important part in the eventual outcome of an established cancer. The circumstantial evidence clearly points to an immunity to tumor which varies to a greater or lesser degree from individual to individual. There is probably a varying immunity to different tumors even in the same individual. The rare but documented instances of spontaneous regression, the demonstration of the ability to produce immunity to transplantable tumors in animals, and the demonstration of circulating tumor cells in the peripheral venous blood of human cancer patients all indicate biologic relationships between the tumor and its host which reflect our presently esoteric concepts of immunogenetics and of immunochemistry.

Early cancer, then, is by no means a simple definition of the physical or temporal extent of a lesion. Dr. L. Henry Garland has calculated that a bronchogenic carcinoma 1 cm. in diameter contains about 33 million cancer cells, assuming the average cell diameter to be $\pm 25\ \mu$, with a range of ± 10 to $40\ \mu$. Under similar conditions, a cancer of the lung which is 2 cm. in diameter would contain 260 million cells. Since a 1 cm. lesion is smaller than a penny-sized "coin" lesion, can a 2 cm. tumor ever be considered an "early" cancer? It seems obvious that mere volume of tumor cells in a given cancer bears little or no relationship to the "earliness" or easy curability of the cancer. A comparison of the clinical possibilities in the management of a cancer of the lip and a cancer of the head of the pancreas of the same size is likewise indicative of the fallacy of believing that a small cancer is necessarily an early one. If one attempts to define any phase of the leukemias as "early," the point is reinforced that the clinical course of the disease and the possibilities of cure or long-term control are what is really meant.

I deplore the fact that, after much thought and soul searching, I cannot really define early cancer, especially since this is the introductory essay for a two day scientific session devoted to discussion of early cancer of various sites and aspects by a group of distinguished scholars. From this intellectually awkward standpoint it would seem to me that we should concentrate our research efforts on lesions which now constitute steps in a descending scale, as it were, of degrees of malignant neoplasia.

If one eliminates invasive cancer from consideration, a definition of early cancer becomes much easier. The obvious condition which then presents itself is so-called *in situ* or preinvasive cancer. Such a histologic change has been recognized in many epithelia, occurring in all areas of stratified squamous epithelium, including skin, lip, oral cavity, pharynx, esophagus, vulva, vagina, uterine cervix and anus. The transitional epithelium of the urinary tract and respiratory epithelium with its squamous metaplasia in the bronchus have also been implicated in this process. In both

the lobular and ductal epithelium of the breast such a change has been demonstrated, and the mucosa of the stomach and colon has produced such cellular mutations.

In all these areas, especially in the uterine cervix, the interpretation of certain cellular changes considered to be preinvasive cancer has been controversial with respect to whether such changes are reversible or will inevitably become invasive cancer. The time lag between recognizing such mutation and the triggering of invasion has been a major factor in the doubts about the concept of *in situ* cancer. Yet, there is a certain core of truth in these considerations that cannot be denied, namely, that most of these lesions can and will undergo inexorable maturation into invasive cancer. It would seem pertinent to ascertain the conditions which determine such maturation, but logically it would be more sensible to find the cause of the original variation in the cellular attitude.

The next step down the scale is therefore the study of the so-called precancerous lesion, such as senile keratosis, leukoplakia, Plummer-Vinson syndrome, atrophic gastritis, gastric polyposis, polyps of the colon and urinary tract papillomatosis, to name a few lesions recognized or suspected as being precancerous.

Even further down the scale of the process of conversion of a normal cell to a malignant tumor, there are background metabolic variations which are only beginning to be appreciated as etiologic or contributing factors. Cirrhosis of the liver has a relation not only to hepatomas but, much more importantly, to the development of cancer of the oral mucous membranes and, quite probably, to the origin of cancer in other sites. The endocrine interplay in a given individual has a bearing on the initiation of neoplasia in certain tissues, as may also avitaminosis and various unrelated conditions causing malabsorption or physiologic misuse of vitamins. It is already apparent that many other etiologic factors are related to the onset of neoplasia. The disciplines of virology and immunology are just entering a crescendo phase of importance in our studies of the basic causes of and reactions to cancer.

As facts accumulate through research in the fields of steroid metabolism and other types of metabolism, viruses and immunochemistry, a pattern should begin to emerge whereby we can start seriously to plan the prevention of cancer rather than to concentrate on destructive attempts to eradicate already established malignant tumors. That this is no idle dream is demonstrated by what has previously been accomplished in prevention of cancer in industry. From Sir Percival Potts and the London chimney sweeps to today's use of saccharolactone to prevent cancer of the bladder in aniline dye workers, there have been tremendous strides in eliminating environmental cancer. There is no purpose in a detailed listing of these successes here, as they are well documented. Suffice it to point out that we know many causes of cancer both pragmatically related to the problem in humans and as a practical tool in laboratory research with animals.

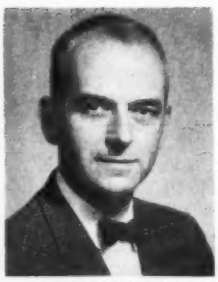
Since we have usually been able to prevent disease when the cause is known and can be eliminated, it would appear that we should greatly intensify our efforts to determine both the direct and indirect etiologic factors related to carcinogenesis. It is more important to prevent than to treat. Until organ transplantation becomes a routine procedure, surgery can accomplish little or nothing more in curing cancer, and the dissemination of cancer defeats both surgery and radiation as modalities in the therapy of this disease.

It is still generally true that the earlier a malignant tumor is diagnosed, the greater is the chance to eliminate it by adequate treatment; nevertheless, it still is preferable that the tumor not occur in the first place. I venture to predict that in the future the most important aspect of cancer management will be prophylaxis. My definition of early cancer, therefore, would simply be "a preventable cancer," and I anticipate an increasing momentum in this phase.

What Is an Adequate "Cancer Checkup?"

EMERSON DAY*

Strang Cancer Prevention Clinic, New York



EMERSON DAY

THE term "cancer checkup" clearly identifies the focus of this paper in the symposium on "Evaluation of early diagnosis of cancer." It is the examination of persons who are presumably well, i.e., without complaints, for evidence of presymptomatic cancer. This is the cancer detection examination which has been emphasized both for the profession and for the public in the intensified cancer control programs of the American Cancer Society, The National Cancer Institute, and related organizations during the past 15 years.

Cancer detection efforts have taken many forms, particularly during the developmental and exploratory phases of the campaign for early diagnosis. There have been single site and "hit-the-high-spot" rapid examination programs, each with its special objective and relative adequacy. Some cancer detection programs have provided what is essentially a complete diagnostic work-up requiring two days and the outlay of several hundred dollars.

As experience has accumulated, the cancer checkup has come to mean that form of cancer detection effort which is oriented to all accessible sites and at the same time is realistic for general practice. It is the cancer checkup which, coupled with a check, forms the basis for current American Cancer Society campaigns for public support and public action in the fight against cancer.

The primary objective of the cancer detection program is the discovery of cancer at the earliest possible stage. The theme is *early diagnosis for cure*. This is based on the working principle that all cancer which originates in a primary focus must, of necessity, pass through a stage at which it is localized in the tissue of origin. At this stage, for most sites, cancer is totally removable by surgery or radiation therapy, and therefore is curable.

An equally important objective for the ultimate control of cancer is the discovery and

*Director, Strang Cancer Prevention Clinic; Chairman, Department of Preventive Medicine, Memorial Center for Cancer and Allied Diseases, New York, New York.

TABLE 1

THE CANCER DETECTION EXAMINATION

History
Family
Environment, habits, illnesses
Review of systems
Physical
Skin and lymph nodes
Head and neck
Breasts
Lungs
Abdomen
Genitalia
Rectum-colon
Extremities
Laboratory
Hemoglobin or hematocrit
White blood cell and differential counts
Urinalysis
Chest x-ray
Vaginal and cervical smears
Tubeless gastric analysis
Stool guaiac

correction of precancerous lesions. These are covered elsewhere in this symposium and will not be considered specifically here.

The Cancer Checkup

Although there are variations of the cancer checkup, it is possible to outline those items in the history, physical examination and laboratory procedures which should be included to assure adequacy according to present-day standards. Table 1 lists the basic elements of the examination as performed at Strang Clinic, Memorial Center, where over 23,000 persons are examined each year.[1,2]

The key features of the Strang cancer detection examination will be discussed in some detail but, first, attention needs to be paid to those ingredients which make for over-all adequacy or success. The first of these is conviction on the part of the examining physician that a cancer detection examination is worthwhile. Based on that conviction, the necessary time must then be set aside by appointment for the complete examination as outlined. The thoroughness which is essential to the adequate examination will be a natural result of the combination of conviction and time.

The experience at Strang Clinic clearly indicates that specialist's training and equipment are not necessary for competent examination. The staff of over 80 physicians and surgeons comes from many types of practice and professional activities. In each instance the patient's examination is provided by a single examiner. Our experience indicates that three-quarters of an hour is a satisfactory time period for the complete cancer detection examination. This includes proctosigmoidoscopy, provided the patient is well prepared. The complete examination is performed in a small booth with simple equipment which is perfectly practical for the private and general office.

History—Family history. The known cases of cancer in the patient's immediate blood relatives should be recorded. Although it is still difficult to obtain a reliable history of the familial incidence of cancer from most patients, ideally one should obtain data in regard to siblings, parents, aunts, uncles and grandparents. The studies of Macklin[3] suggest that the familial history of cancer, even as obtained from intelligent patients, tends to underrecord the actual incidence of histologically proved cancer by a factor of 1 to 3.

Environmental history. This should include major places of residence, i.e., whether rural or urban, and a record of any occupational exposures to known carcinogens such as certain petroleum products, aniline dyes, chromate, nickel, asbestos, or unusual sources of radioactivity.[4,5] The habits of smoking, particularly cigarettes, and drinking are important historical data. For women, the past history should include a record of menstrual, obstetric and nursing data. It is also wise to record any unusual history of drug or hormone intake, although none has been specifically proved to have carcinogenic activity.

Review of systems. A thoughtful review of systems is essential, even in the patient who has asked for a cancer checkup with the typical, "Oh, I am fine, doctor, I just want a checkup." Occasionally, obviously significant abnormalities are encountered which, though disregarded by the patient, have medical significance. In addition, a thoughtful review of systems may uncover slight changes from the

"norm" such as a low-grade cough or mild changes in digestive or bowel patterns. These may prove to be important though subtle diagnostic leads.

Preprinted forms and questionnaires designed for self-administration by the patient can be helpful in sparing professional time in the categories of family and personal past history. The review of systems, however, requires a face-to-face history taken by the examining physician.

Physical examination—A large part of the examination's success depends on careful inspection and palpation. These are the essential ingredients for adequate examination of the skin, node-bearing areas, head and neck region, breasts and external genitalia. Special application of technics should be incorporated in the examination of the oral cavity, hypopharynx, larynx, and the pelvic and rectal-colon examinations. The key features are as follows:

Skin and soft tissue. While all areas of the skin surface should be examined, those marked for particular attention include the sun-exposed surfaces, the palms and soles, the genitalia, and the areas subject to repeated trauma, i.e., the shaving areas and the area of shoulder straps and underclothing pressure in women. All suspicious lesions located in those areas require excisional biopsy for histologic diagnosis. Only in this way, for example, can a differentiation be made between the innocent dermal nevi and those of junctional nature which carry the special import of being forerunners of melanoma.[6] The feel of a skin lesion on palpation and its appearance or color on inspection are not adequate for diagnosis. Only the microscope can determine its true nature.

Head and neck. For the inspection of the head and neck area, both external and internal, good lighting is essential. This is best provided by the head lamp with electric bulb rather than the old-style reflection mirror. The examination starts with inspection of the skin and mucous membranes, followed by palpation of the accessible portions of the oral cavity and tongue. This is best accomplished with the forefinger covered by a finger cot. The hypopharynx and vocal cords can be visualized with the laryngeal mirror in approximately 75 per cent of patients without the need for local anesthesia and should be included regularly in the head and neck examination.

Figure 1, step 5, shows the extent of the areas which require palpation for enlarged lymph nodes. The finding of adenopathy in an adult, when infection is not an obvious cause, is evidence of carcinoma until proved otherwise. Lymph node enlargement in the upper cervical chain points suspicion at the nasopharyngeal and tonsillar area. In the mid-cervical area the larynx and thyroid must be intensively investigated. In the lower nodes the thyroid and infraclavicular sites must be suspected.

As a general policy it is important to search thoroughly for a primary lesion in these areas before contemplating biopsy of the lymph nodes. If no primary tumor can be located by intensive diagnostic investigation of the areas of suspicion, then removal of a representative lymph node by total surgical excision is the procedure of choice. In some hands needle aspiration of lymph nodes for diagnostic purposes has proved to be a useful procedure, but the pathologic interpretation is often difficult and the findings equivocal.

The thyroid gland can be palpated from in front of the patient or from behind, depending on the examiner's habit pattern. The important aspect of the examination is that it include both lobes and the isthmus and that the examiner be feeling "in his mind" for nodules which may be only a few millimeters in diameter. The size and number of nodules are not determining factors in the significance of thyroid findings. Both small single nodules and larger nodules in multiplicity may be associated with carcinoma of the gland. The experience at Strang Clinic, where the policy is to advise surgical removal of all palpable nodules of the thyroid, has demonstrated the fact that a preoperative impression of benignity does not assure the absence of carcinoma. This experience is consistent with that of many other clinics and emphasizes the point that, until preoperative diagnostic methods are more precise, an adequate cancer detection

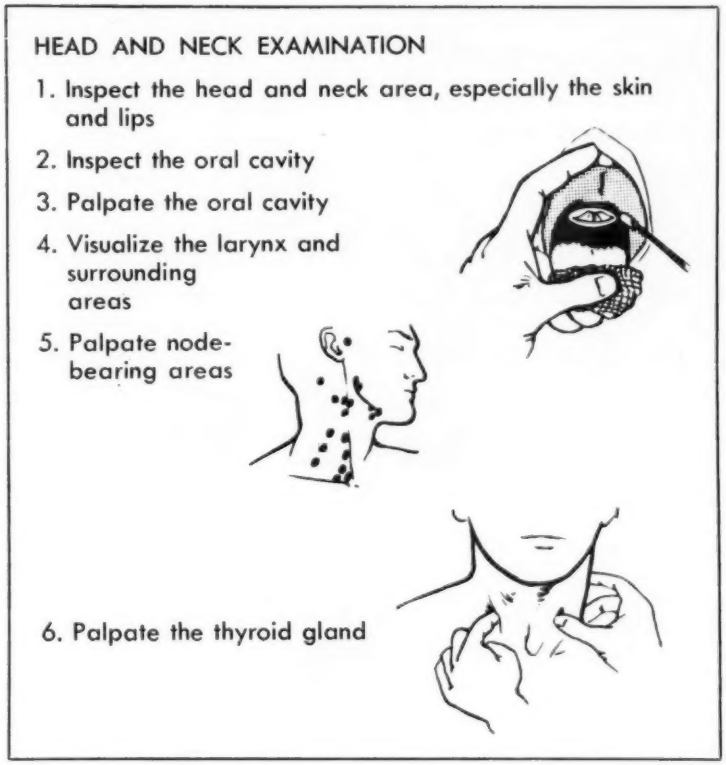

HEAD AND NECK EXAMINATION
1. Inspect the head and neck area, especially the skin and lips
2. Inspect the oral cavity
3. Palpate the oral cavity
4. Visualize the larynx and surrounding areas
5. Palpate node-bearing areas
6. Palpate the thyroid gland

FIGURE 1.

program requires a policy of surgical approach to all palpable nodules of the thyroid without waiting for the clinical findings which suggest carcinoma.

Breast. As outlined in figure 2, inspection is made with the patient sitting, facing the examiner. Good light, without shadows, is essential. The contour and symmetry of the breasts are noted with arms relaxed at the side, with arms raised, with pectoral muscles tensed, and with the patient leaning forward. The pectoral areas and axillae are best examined during this part of the procedure. Thorough palpation of the breast tissue is best performed while the patient is supine with the arm raised and shoulder elevated or body turned slightly so that the breast tissue is distributed evenly over the chest wall. In this position all quadrants are palpated methodically using firm but gentle pressure of the flat of the fingers. Special attention should be paid to the subareolar tissue and to the nipples. Any yellow or dark or bloody nipple fluid should be submitted for cytologic examination and the axis of the duct from which it originates carefully noted for possible surgical exploration.

Monthly self-examination of the breasts by an instructed patient is one of the most effective means of improving the early diagnosis of breast tumors. Demonstration of the technics of self-examination can be incorporated by the doctor as part of a cancer checkup and can be aided by lay educational material such as the film "Self-examination of the breast," distributed by the American Cancer Society.

Lung. The most effective tool for the detection of silent tumors of the lung is the chest x-ray. In high-risk groups, cytologic examination of bronchial secretion is a valuable adjunct when sputum specimens can be obtained spontaneously or by use of aerosol inhalation.[7] Physical examination of the lungs should be

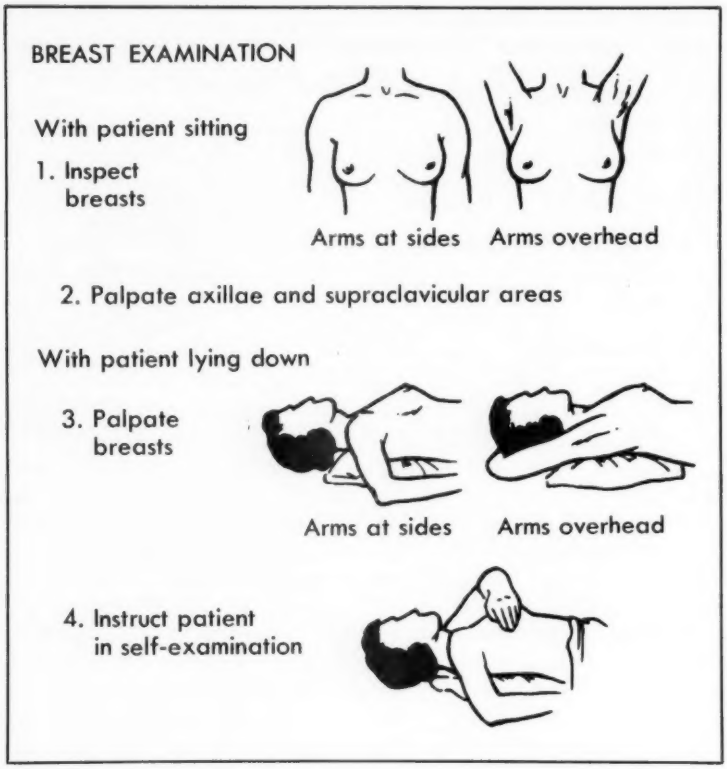


FIGURE 2.

included in a cancer checkup, since occasionally failure of a pulmonary segment to aerate normally and a unilateral wheeze are the first evidence of a partially obstructing bronchial tumor.

Abdomen. Careful palpation of the abdomen may reveal an otherwise unsuspected mass or enlarged viscus. While hepatic enlargement due to cancer is generally a discouraging finding, an intra-abdominal mass or an enlarged kidney detected on abdominal examination may be the first evidence of a tumor which is still at a potentially curable stage.

Female genitalia. Figure 3 outlines the cancer detection examination of the female reproductive organs. Adequate surveillance for early cancer and its precursors requires both careful pelvic examination and the taking of cytologic smears. Neither alone is adequate, but together they form a simple and highly effective standard office procedure. The routine which has proved satisfactory at Strang Clinic is as follows:

1. Inspect external genitalia. Note introitus and any abnormalities of skin, mucous membranes, glands and urethra.

2. Vaginal smear. Aspirate posterior and lateral fornices with vaginal pipet. (Patient should be pre-instructed not to douche for 48 hours.) Spread secretion evenly on a glass slide and place *immediately* in bottle of fixative made up of ether and 95 per cent alcohol in equal parts. It is important that the aspirator bulb and slide be free of water and that the smear not be allowed to dry before fixation.

3. Internal inspection. Insert speculum without lubricant. Inspect vagina and cervix with good light, preferably from head lamp. Note character of vaginal discharge if present.

4. Cervical smear. Swab entire cervical surface with cotton applicator, then insert and rotate applicator inside cervical os. Roll appli-

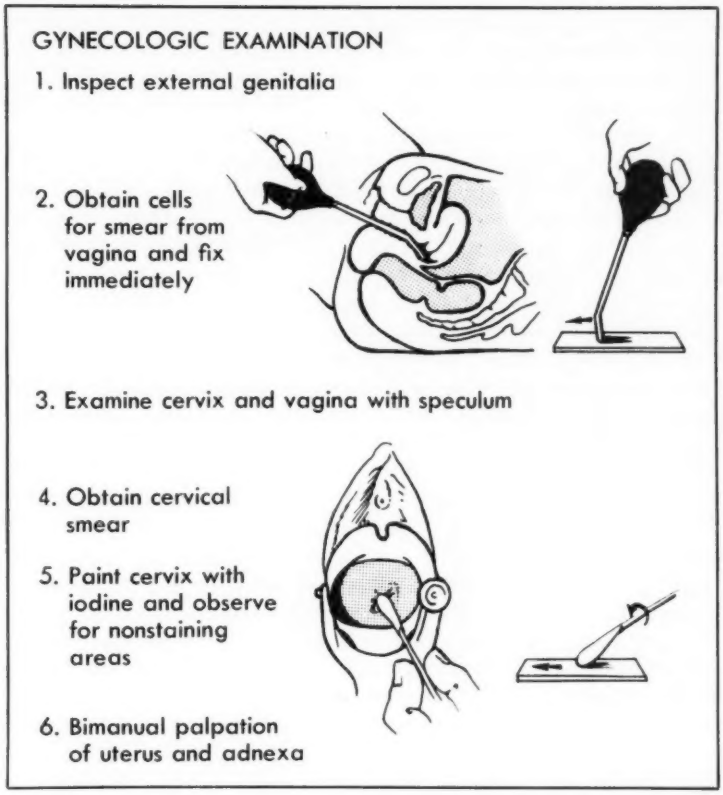

GYNECOLOGIC EXAMINATION
1. Inspect external genitalia
2. Obtain cells for smear from vagina and fix immediately
3. Examine cervix and vagina with speculum
4. Obtain cervical smear
5. Paint cervix with iodine and observe for nonstaining areas
6. Bimanual palpation of uterus and adnexa

FIGURE 3.

cator on slide, making a thin, even smear. Put slide immediately in ether-alcohol solution.

Figure 3, steps 2 to 4, illustrates the taking of vaginal and cervical smears by the Papanicolaou method. Other means of obtaining material from the cervix, such as the cervical scrape, may be substituted for the swab technic if the laboratory receiving the material is acquainted with the method. In all cases the cytologist should be given clinical data in regard to menses, hormone or other gynecologic therapy, pregnancy and infection, since these factors may be associated with cytologic changes.

In addition to the routine smears listed, endocervical and endometrial aspiration smears using a special aspiration cannula[8] have proved to be a practical and useful office procedure in the presence of (1) a history of abnormal bleeding, (2) enlargement of the uterus, or (3) blood on the cotton swab when the routine cervical swab smear is taken from the external os.

5. Iodine test. Do not perform the test if patient gives a history of iodine sensitivity. With cotton applicator apply 7 per cent (strong iodine, N. F.) tincture of iodine to cervix. Note position and size of nonstaining areas.

Biopsy any suspicious area using punch forceps. Significant sites are those which are completely unstained by iodine, in contrast to the frequent poorly stained mucosal surfaces. Areas of leukoplakia, which appear white on direct examination, should also be biopsied. Include a portion of adjacent uninvolved tissue in biopsy specimen, and identify site on clinical record and for pathologist.

Hemostasis is usually not a problem if a sharp punch is used. Hold gauze pledget soaked in hydrogen peroxide firmly against

cervix for one to two minutes and insert tampon. If bleeding persists apply GELFOAM® or use electric cautery on bleeding point.

6. Bimanual examination. Standard palpation of pelvic organs is an essential part of all female cancer detection examinations. Include fornices and adnexa as well as cervix and fundus, and end with combined rectovaginal examination.

Cervical cancer detection. Vaginal-cervical smears properly taken and interpreted, combined with biopsy of all suspicious areas, will detect essentially every case of carcinoma of the cervix. In a series of 102 cases at Strang Clinic approximately 90 per cent were *in situ* or preinvasive cancer; 53 per cent were detected as a result of the routine smear before there were clinical findings by history or pelvic examination.[9] In cases with a suspicious or positive cytologic report and a normal-appearing cervix, four-point biopsies are taken as recommended by Foote and Stewart.[10] This simple office procedure will reveal the site of over 90 per cent of early cervical carcinomas and avoids the necessity for hospitalization inherent in cone biopsy technics. Cases with repeated abnormal smears and no focus of cancer demonstrable by office biopsy should be referred to a specialist for management. It is important that no cauterization or other treatment be undertaken at the first examination, or until cytologic and pathologic reports are received, in order not to obscure a lesion and confuse subsequent care.

Male genitalia and prostate. The external male genitalia are readily available for thorough inspection and palpation, yet it is impressive how often this is not a standard part of a cancer checkup. In assuring an adequate examination it is important that the foreskin be stripped back for thorough inspection of the glans in uncircumcised males. Adequate evaluation of the testis may require aspiration or removal of a hydrocele, which is particularly noteworthy if this has been of recent development in an adult.

Digital palpation through the rectum is a primary means of detecting early cancer of the prostate and should be routine in the examination of every adult male. Cytologic smears of prostatic fluid obtained by massage and tests of serum acid phosphatase levels are helpful diagnostic adjuncts but are not useful for screening purposes. The significant finding on digital examination is classically described as a firm to "stony hard" area or nodule. To this should be added localized areas of altered consistency within the gland. While such findings may be due to calculus, chronic infection or adenoma, success in the detection of prostatic cancer requires that carcinoma be listed as the diagnosis of first importance and increasing probability after the age of 50. Histologic diagnosis must be insisted on, based on competent pathologic examination of the entire nodule or suspicious area obtained by direct surgical excision. Blind needle or partial biopsy cannot be depended on, since a negative finding does not rule out carcinoma.

Rectum and colon. The rectum and distal colon become accessible and highly productive sites for cancer detection by the routine practice of two procedures, digital examination of the rectum and proctosigmoidoscopy (figure 4).

Digital examination of the rectum should be routine in every physical examination. Even good digital examination, however, will miss early mucosal and soft polypoid lesions. It cannot be depended on to rule out disease of the rectum and is not an adequate detection procedure alone.

Proctosigmoidoscopy permits visualization of the mucosa of the rectum and sigmoid colon and biopsy of any lesion seen. It thus meets the basic requirements for successful cancer detection, namely, direct access with opportunity for pathologic examination of tissue specimens when indicated.

Proctosigmoidoscopy is a simple and safe office procedure. It requires no more than five minutes if the lower bowel has been well cleansed. The standard knee-chest position (figure 4) is most satisfactory from the examiner's point of view, although the lateral Sims position is useful when the more strenuous knee-chest maneuver is undesirable.

The best sigmoidoscope for detection work is 10 in. long with a diameter no greater than ⅝ in. With any model scope of these dimen-

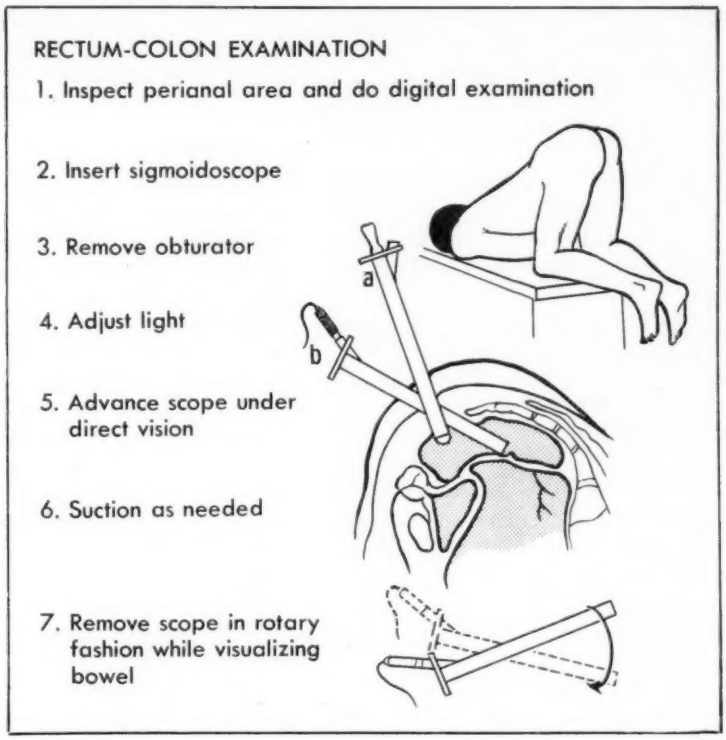

RECTUM-COLON EXAMINATION
1. Inspect perianal area and do digital examination
2. Insert sigmoidoscope
3. Remove obturator
4. Adjust light
5. Advance scope under direct vision
6. Suction as needed
7. Remove scope in rotary fashion while visualizing bowel
a
b

FIGURE 4.

sions visualization of the bowel mucosa should be accomplished to a distance of 25+ cm. in most patients. The instrument is advanced always with the lumen of the bowel in direct vision and without using force. Thorough inspection of all mucosal surfaces is accomplished while the sigmoidoscope is being withdrawn by use of a rotary motion (figure 4, step 7). Insufflation of air should not be used unless necessary to flatten out folds of mucosa.

The most common lesion encountered on proctosigmoidoscopy is the rectal or colon polyp. All such lesions should either be biopsied or removed *in toto* for microscopic diagnosis. Biopsy can be accomplished safely at the time of routine examinations by use of a small-cup forceps through the sigmoidoscope, as long as the base of the polyp is avoided. Histologic diagnosis is imperative since a significant number of polyps will prove to be early cancer or will show premalignant changes.[11]

For the detection of lesions of the colon beyond the reach of the sigmoidoscope, all patients with mucosal lesions at proctosigmoidoscopy and patients with symptoms or laboratory evidence of any bleeding are routinely referred for barium enema with air contrast studies. X-ray examination without air contrast studies is totally inadequate in the search for small polypoid lesions. The determination of the nature of tumors or lesions proximal to the sigmoid may be aided by colonic washings for cytologic study but will often require laparotomy for definitive diagnosis.

Laboratory examinations—Blood and urine. A determination of hemoglobin level or hematocrit is an essential feature of an adequate cancer detection examination, since unexplained anemia may be the first evidence of occult cancer, particularly of the gastrointestinal or urinary tract. As a general rule the red blood cell count is to be avoided for this purpose because it is more time-consuming and

less accurate than either hemoglobin or hematocrit determination. If these are abnormal, a full hemogram can be undertaken.

White blood cell count and differential smear may provide the first evidence of lymphoma or leukemia.

Urinalysis should include microscopic examination of the centrifuged sediment, since microscopic hematuria may be the presenting evidence of presymptomatic tumors of the urinary tract.

Chest x-ray. X-ray examination is the most effective method of screening for lung cancer. Experience has demonstrated that properly read films (either standard size or screening minifilms) will pick up the majority of early tumors of the lung. Chest x-ray should be performed routinely on all initial cancer detection examinations and annually on patients over the age of 45. Fluoroscopy is not an acceptable substitute for the chest film, since it is not as accurate for small lesions, entails substantially more radiation exposure, and, most important, it does not provide a record for comparison on subsequent examinations.

Vaginal and cervical smears. Recent mass screening programs have reported that from 60 to 100 per cent of patients with a histologic diagnosis of cervical carcinoma were clinically unsuspected and were detected only on the basis of routine vaginal-cervical cytology.

Tubeless gastric analysis. Studies, particularly those of Wangensteen and his group in Minnesota,[12] have demonstrated improved detection rates for asymptomatic gastric tumors by the use of prescreening for achlorhydria. While the original studies used direct intubation, which is generally not acceptable for detection examinations, the development of a method for tubeless gastric analysis* now makes this a simple office procedure.[13]

Stool guaiac. Routine examination for occult blood of the stool obtained on the examining finger may be useful in signaling the presence of gastrointestinal bleeding due to cancer of the rectum and colon, as well as elsewhere in the bowel. This positive finding should always be checked by having the patient submit at least one repeat stool obtained following a three day meat-free diet; if this is still positive, complete radiologic examination of the gastrointestinal tract is then in order.

*Available as DIAGNEX® Blue, E. R. Squibb & Sons.

Adequacy

In judging the adequacy of a cancer checkup one must weigh effort expended against results obtained. The left side of the equation, or input, includes the physician's time and that of his office personnel and of the patient and the cost of office and laboratory x-ray procedures. All these must be utilized efficiently to keep the balance favorable. On the other side of the equation rests not only the count of cancers and precancers found but also the specific importance of their detection in terms of cancer control. I shall not attempt an analysis of these interrelated factors at this time, but would like to emphasize certain pertinent aspects of the effort-versus-yield equation.

Professional time is the most critical investment in cancer detection examinations. There are several ways to conserve it.

1. A systematized examination procedure should be established with appointments synchronized to the office sequence. Preprinted forms are helpful in assuring a smooth-flowing complete examination and useful records.

2. A screening history can be an important aid to professional efficiency. Not only does it spare the physician from involvement in obtaining background "diary-type" data, but a self-administered form may improve the quality of the family and personal past history when completed by the patient at home prior to the office appointment.

3. Facilities for those laboratory or x-ray procedures which must be provided outside of the office should be prearranged. Community or group services improve office efficiency and often allow a lower unit cost for standard detection procedures such as vaginal-cervical smears and chest x-rays.

4. The demand on the doctor's time can be controlled and its effectiveness in terms of cancer detection enhanced by concentrating efforts on those individuals with relatively higher cancer risks. Table 2 lists a number of "selection factors" which are useful in cate-

TABLE 2

CANCER DETECTION EXAMINATION: SELECTION FACTORS

Sex and age
Female, 30 and older
Male, 40 and older
Family history of cancer or precancer
Past history of cancer or precancer
Environmental exposures
Smoking
Industrial hazards

gorizing those patients who should have priority attention.

The other side of the equation, namely, the yield of the cancer detection program and its value for cancer control, requires an analysis of resulting diagnoses and the effect on mortality. The number of cancers diagnosed as a result of cancer detection examination will vary with the nature of the population examined. In general, age and sex are the prominent determining factors. At Strang Clinic approximately eight per thousand women and six per thousand men are found to have cancer on initial examination.[14] This is in a population over two-thirds of whom are below the age of 50. The same[15] or a similar[16] detection examination in persons above the age of 50 yields cancer in over 1 per cent of examinees.

The asymptomatic unsuspected cancer found in the cancer detection program is in large part localized and presents a high expectation of cure. To such cancer yields must be added those precancerous findings such as polyps of the rectum and colon, cervical atypias, certain mucosal leukoplakias, etc., the control of which should lead to actual cancer prevention.

The final significance of these results of cancer detection examinations in terms of improved cancer death rates will be determined only after long-term follow-up studies. These are now being conducted at Strang Clinic and other places. Meanwhile, a partial rough estimate of the potential effects of cancer detection on cancer mortality was obtained by posing the following hypothetical question to members of the professional staff of Strang Clinic: What proportion of current cancer deaths would not occur if all of the adult population had a periodic cancer detection examination of the type outlined?

Table 3 is the result of this exercise, based on the United States cancer deaths for 1957. In the left-hand column are listed the six major sites followed by head and neck and skin which, though of lower mortality, are accessible targets of the cancer detection program. The second column lists the 1957 cancer deaths to the nearest 500. In the middle column, titled "Per cent preventable," is given for each site the pooled estimate of those examining physicians and consultants to whom

TABLE 3

THE POTENTIAL EFFECT OF CANCER DETECTION ON CANCER MORTALITY BASED ON UNITED STATES STATISTICS, 1957

SITE	1957 MORTALITY	PER CENT PREVENTABLE	REVISED MORTALITY	SALVAGE
Colon-rectum	37,500	65	13,125	24,375
Lung	31,000	10	27,900	3100
Breast	23,000	50	11,500	11,500
Stomach	21,500	10	19,350	2,150
Uterus	15,000	80	3000	12,000
Prostate	14,500	50	7,250	7,250
Head and neck*	9000	50	4500	4500
Skin†	2000	100	—	2000
Totals	153,500	43.6	86,625	66,875

*Includes buccal cavity, pharynx, larynx and thyroid.
†Not including melanoma.

the hypothetical question was presented. The fourth and fifth columns are derived by simple arithmetic once the "per cent preventable" figure has been decided on.

The attempt in these estimates of the potential effects of a universal cancer detection program was to remain conservative. There is an obvious shortcoming in this exercise since mortality rather than incidence figures were used. This was done purposely since reliable United States incidence figures are not available and the inherent bias was kept in mind in estimating salvageability.

Any estimate of cancer deaths which could be prevented by early diagnosis is obviously tentative for lung, breast, stomach and prostate. However, the exercise is a useful one if only to erect a target for discussion purposes and subsequent correction as analyzable experience becomes available. Acquaintance with the nature of the disease allows one to state with fair certainty that cancer of the cervix and cancer of the skin (excluding melanoma) could be essentially removed from the list of causes of death, and cancer of the rectum-colon greatly reduced, by a program of cancer detection. The big "if" is not the effectiveness of the examination in these areas but the means of providing this type of examination for the adult population. A strong impetus for getting on with the job lies in the conviction that a substantial reduction in cancer deaths can be accomplished by the application of simple technics in office practice without waiting for further research or the development of a miracle cancer drug.

ACKNOWLEDGMENT

The author is indebted to Dr. Walter E. O'Donnell, Assistant Director, Strang Clinic, for figures 1 to 4. The faithful and highly effective services of the professional and administrative staffs of Strang Clinic are also gratefully acknowledged.

REFERENCES

1. Day, E.: Early diagnosis of cancer. M. Clin. North America 38:639-654, 1954.
2. O'Donnell, W. E. and Day, E.: Early cancer—its detection, diagnosis and management. *Ibid.* 40:591-610, 1956.
3. Macklin, M.: Inheritance of cancer in men. Schweiz. Ztschr. allg. Path. 18:463-471, 1955.
4. Rhoads, C. P., O'Donnell, W. E., Nickson, J. J., Southam, C. M. and Whitmore, W. F., Jr.: Symposium and panel discussion: Some present concepts of carcinogenesis. New York J. Med. 59:2154-2168, 1959.
5. Wynder, E. L.: Environmental causes of cancer in men. M. Clin. North America 40:629-645, 1956.
6. Allen, A. C. and Spitz, S.: Malignant melanoma: A clinicopathologic analysis of the criteria for diagnosis and prognosis. Cancer 6:1-45, 1953.
7. Bickerman, H. A., Sproul, E. E. and Barach, A. L.: An aerosol method of producing bronchial secretions in human subjects; clinical technique for the detection of lung cancer. Dis. Chest 33:347-362, 1958.
8. Jordan, M. J. and Bader, G. M.: New cannula for obtaining endometrial material for cytologic study. Obst. & Gynec. 8:611-612, 1956.
9. Day, E. and Bader, G. M.: Unpublished data.
10. Foote, F. W., Jr. and Stewart, F. W.: The anatomical distribution of intraepithelial epidermoid carcinomas of the cervix. Cancer 1:431-440, 1948.
11. Hertz, R. E. L., Deddish, M. R. and Day, E.: Value of periodic examinations in detecting cancer of the rectum and colon. Postgrad. Med. 27:290-294, 1960.
12. Hitchcock, C. R., Sullivan, W. A. and Wangensteen, O. H.: Value of achlorhydria as a screening test for gastric cancer; 10-year report. Gastroenterology 29:621-632, 1955.
13. Segal, H. L. and Glaser, G. L.: Early detection of gastric carcinoma. New York J. Med. 56:237-240 (January) 1956.
14. Venet, L. et al.: Unpublished data.
15. O'Donnell, W. E.: Experience with a cancer detection program for senior industrial employees. A.M.A. Arch. Indust. H. 18:278-280, 1958.
16. Shahon, D. B. and Wangensteen, O. H.: Early diagnosis of cancer of the gastrointestinal tract. Postgrad. Med. 27:306-311, 1960.

The Changing Responsibility of the Practicing Physician in Cancer Detection

I. PHILLIPS FROHMAN

Washington, D.C.

"Suspicion is our greatest diagnostic tool!"

I. PHILLIPS FROHMAN

SOME years ago, when a practicing physician established a diagnosis of cancer, it was usually in the easily detected later stages, and when the diagnosis was made, the patient was referred to the surgeon for whatever he could do to aid the patient. At this point the practicing physician's responsibility usually ended until the surgeon returned the patient to the referring physician to care for him until his demise.

In most instances patients came to the doctors only when they had noticeable symptoms, such as heavy cough, hoarseness, blood in the sputum, stool or urine, constant stomach or intestinal upset or pain, weight loss, or when they were unable to continue with their daily work. Doctors, some years ago, were called on to "cure" or remedy a definite illness which brought the patients to their offices.

Fifteen or 20 years ago, family physicians and some specialists did just that—examined and treated patients for their specific complaints and for not much else. Today, the attitudes of both physician and patient have changed greatly in respect to physical examinations and general care. Students of medicine and practicing physicians have been trained to do more thorough examinations on all patients, irrespective of their perhaps very simple complaint. The patient who comes to the physician today complaining of a headache should receive as comprehensive an examination as the patient who comes to us with the complaint of "I just don't feel right, yet nothing specific is bothering me." In the latter case the interested physician will do a thorough examination and search for the obscure cause of this nonspecific complaint, while in the case of the patient complaining of headache a superficial examination for high blood pressure might be the only examination. This might be followed with a prescription for a few headache pills and the patient's being sent on his way. This patient might be the one with the brain tumor.

We physicians must not be too glib or smug

when we finish a complete physical and laboratory examination and find absolutely nothing wrong with the patient, nor must we attribute all of our supposedly "normal" patients' complaints to their nervousness or to simple psychosomatic disorders. Recently I saw a patient with a very simple complaint. She had had a head cold with right frontal sinusitis and some right-sided facial pain. Complete physical examination revealed only a slight sluggishness of the right pupil and extreme nervousness. Nothing else. After the complete physical examination, I referred her to an ophthalmologist who likewise found nothing to worry about except the sluggish pupil, but he believed that this would return to normal in a few days. Two days later this patient came to me with slight ptosis of the right upper lid. I discussed this finding with the ophthalmologist and neither one of us had any answer. I was still unhappy at my ignorance as to the cause and so decided to refer her immediately to a neurosurgeon. Examination by him again revealed nothing. Numerous x-rays and arteriograms of the head finally revealed that this patient had an aneurysm of the right internal carotid artery. Surgery was immediately performed with ligation of the right internal carotid artery, and this patient had an uneventful recovery.

I present this case merely to bring out the point that all persons, including ourselves, may be somewhat nervous and upset when not feeling up to par. Simple complaints or minor symptoms must not be dismissed.

Whenever I talk to various groups of people in Washington, D. C., for the American Cancer Society, it unfailingly happens that several women come up to me after the cancer movie is shown and the question and answer period is over and tell me that they just had a physical examination and that a cancer smear or a breast examination had not been done. This is incredible!

Thorough examination of the patient is the basis of good medical practice. If the practicing physician does not perform any of the accepted tests, such as cytologic study of the cervix, sigmoidoscopy, and others within his power and ability, then he must refer those patients to someone who will do them. Even when the chief complaint is well localized, a complete examination may disclose diagnostically important clues or other findings which are important to the patient's welfare. The periodic checkup should try to unearth clues to disease early in the beginning of the disease. This is good preventive medicine. The closer we observe and the more we seek, the more we will find. The aneurysm of the carotid, the carcinoma *in situ* of the cervix, the silent coin lesion in the lung, the apparently innocent melanoma, and many other quiet precursors of fatal disease and cancers are the things the present-day physician must be looking for.

The changing responsibility of the practicing physician to his patients today is manifold. Health education of the patient by the doctor is of foremost importance. Education in proper and necessary diet,[1,2] in the dangers of cigarette smoking, knowledge of hygienic measures in the care of the vagina and the care of the penis in the uncircumcised male, protection against industrial vapors and dusts, proper care of the female breasts, and training in breast self-examination are but a few of the many ways in which the physician of today plays the role of health officer and teaches preventive medicine to his patients.

A complete physical examination as we know it today was quite unheard of in general practice 20 years ago. Basically, these important steps must be undertaken for actual completeness of the examination: survey of the completely disrobed patient from head to foot; next, careful examination of the eyes, ears, nose, throat and mouth, then the heart and lungs, including x-ray of the chest; examination of the breasts, abdomen, and anal region, including a digital examination of anus and rectum; sigmoidoscopy; pelvic examination and cervical cytology in females; blood studies, including blood counts, cholesterol, sugars; complete urinalysis; neurologic and other examinations the physician feels he needs to do to unearth underlying disease or cancer.

The physician can accomplish most of the examinations mentioned which comprise a complete physical examination as we know it at the present time. If the physician is not

trained to do x-ray diagnosis, or if he does not have the equipment for laboratory tests, he should send his patients elsewhere for these examinations or tests. In most instances the hospital laboratory or private laboratories under the management of a qualified pathologist will do the various examinations of the blood, urine and feces and cytologic examinations at a reasonable cost. In cities where cancer detection centers exist, patients may be referred to them for examinations at a modest fee. The results of such examinations are reported to the referring physician and the patient returns to him for further care and treatment. The cancer clinic should and will give the referring physician the opportunity to select consultants for his patients whenever disease or cancers are found in any patients who were seen and examined at these cancer clinics. In my own city, the District of Columbia, we are most happy with our relationship with the cancer clinics and the fine work they do for the patient and the referring doctor.

Today it is not enough to establish the diagnosis of cancer. To be of benefit to the patient and to advance the over-all effectiveness of cancer control, the diagnosis must be accomplished while the disease is still localized and amenable to cure by complete eradication through surgery, radiotherapy, or the combination of both. No longer can the physician or the patient "wait and see," for the things that might and usually do develop are widespread metastases, followed by death. Good prognosis depends on early diagnosis.

Routine chest x-rays are indispensable. If the patient's blood pressure, urine and blood are checked, in the same motion one must go one step further and request a chest x-ray. Let me show you the importance of chest x-rays on apparently healthy patients visiting your office and mine. In a paper published in 1953,[3] I advocated that it should become routine and required practice to take a chest x-ray film of every patient admitted to a hospital. In this same report I compared the April and May (1952) findings of the mobile unit operated by the District of Columbia Tuberculosis Association for a six week period in my section of the city. In this period of six weeks, 10,830 chest films (microfilm) were taken of both males and females whose ages ranged from 15 to 45 years and who had come voluntarily to the mobile unit. Of the 10,830 microfilms taken, 511 were retaken at the clinic on 14 by 17 in. film. The findings in the latter group of films led to more complete examinations of 165 persons, including sputum examination, sedimentation rate and other tests. Twenty-seven cases of tuberculosis in one type or another were uncovered, but only 10 cases of active tuberculosis; of these 10 only three patients needed hospitalization. This is approximately one-tenth of 1 per cent, a small figure for so large an investment.

I then reviewed my office records of the number of chest x-rays I had done on my apparently healthy patients in the 3 to 76 year age group for the first six months of 1952. The percentage of tuberculosis discovered was 4.4 per cent.

If we consider the disparity between the percentages in these two groups, it is sufficient cause for contemplation and reflection by all physicians, and particularly general physicians. What I have said about tuberculosis applies equally to cancer of the lung. To wait for obvious symptoms of lung cancer is foolhardy, and the idea promoted by the scientists to discontinue x-rays for fear our patients might become excessively irradiated is sheer nonsense. There is more irradiation from one exploded atomic bomb than from all x-rays patients have in a lifetime.

Our responsibility as physicians consists in educating our patients that proper and necessary x-rays and the valuable findings uncovered by them far outweigh any possible harm from the amount of irradiation thus received.

The vital and responsible role of the practicing physician today is to heed and investigate even minimal symptoms and to perform at regular intervals routine complete physical examinations with special reference to the key sites mentioned before.

The various cancer detection methods, the equipment necessary, and the procedures in office examinations have been outlined in many fine papers over the years. It is not my purpose to repeat what has been so ably writ-

ten by many physicians in the field of cancer diagnosis and treatment.

Exfoliative cytology has made very rapid advances in the past decade and may justly claim its rightful place among the morphologic sciences. Its general acceptance as a standard procedure for diagnosis is attested by its widespread use. The most important use and contribution of the cytologic test is that it permits the diagnosis of cancer in its earliest stages prior to the appearance of any clinical manifestations of the spread of the disease. The cytologic test as originally demonstrated by Dr. Papanicolaou was limited to the female genital tract, but during the past decade secretions from many other parts of the body have been subjected to cytologic scrutiny for cancer, such as sputum and bronchial washings of the lung; urine; washings from the esophagus, stomach, duodenum and colon; secretions from the nasopharynx, prostate and breast; and washings from the pleural, peritoneal and pericardial cavities which have lately been added to the list. I believe that cytologic diagnosis is a most wonderful tool for the practicing physician. This test, more than any other diagnostic procedure, has greatly changed the responsibility of the practicing physician in the past 10 years. Today, the practicing physician must find the early signs of cancer prior to invasion rather than the late manifestations, when all the patient needs is terminal treatment and the services of the mortician. I firmly believe that the vast majority of physicians are doing their job and duty toward their patients in this respect.

The cytologic test for cancer certainly stands as one of the most important and brilliant achievements in cancer detection and diagnosis. Yet, it is quite evident to all physicians that even this test cannot be performed on the vast majority of our population, not even the female portion where it is applied so easily. This is not due, in most instances, to the fault of the practicing physician but rather to the lack of interest that people have in themselves as frail humans, subject to cancer. A new home, a fine television set, a new car and washing machine are often of more importance than finding cancer and disease in their bodies. In view of this patient-negligence and in spite of all the fine work of the American Cancer Society in this field, something more and much greater is needed to help the practicing physician to detect cancer much earlier than we are able to at the present time.

In spite of the great advances in surgical technics and the wonderful training afforded surgeons in many large hospitals and cancer centers in the field of thoracic surgery, the survival rate in cancer of the lung remains a pitiful and meager 5 per cent. This is not the fault of the physician or surgeon, nor is the patient to be blamed. It is our lack of some diagnostic instrument or new concept that would help in the very early diagnosis of this malignancy.[4]

Again, our survival or salvage rate in cancer of the female breast depends not so much on the surgeon alone but primarily on the time of diagnosis—early or late.[5] The disappointing experiences reported in the literature by numerous surgeons attest to the frightening fact that more than one-third, and perhaps as many as one-half, of the breast cancers which seem definitely localized in the breast already have impalpable axillary metastases and some of these metastases may extend beyond this boundary.[6]

We physicians need a generalized and overall test for cancer detection. This responsibility lies in the hands of the research physicians and the research scientists. These two groups must come up with perhaps precision instruments which could measure chemical and biologic materials of the blood and lymph so that the mere offering of a blood sample taken from the patient and sent to the laboratory for chemical analysis would tell us at once (1) if the patient is cancer-prone or cancer-potential, (2) whether the patient has dormant cancer cells shedding noncancerous by-products into the lymph or blood stream, and finally (3) the area or portion of the body from which these cells emanate. I realize that this would be the Utopia of cancer detection.

Certainly, this is the dreamer's paradise of cancer detection, but I predict that, perhaps in the not too distant future, with the continued union of the many scientific disciplines

n the search for understanding of the mystery f life, and the nature of normal and abnor- nal growth, there will evolve from the proper blending of biology, chemistry and physiology with virus oncology, radiobiology and chemo- therapeutics just such a test.

The changing responsibility of the practic- ing physician, the research physician and the research scientist is the responsibility of can- cer prevention. All of us have been educated in cancer detection and cancer eradication. Over 98 per cent of the literature on cancer published in the journals has to do with either cancer detection or cancer eradication after the diagnosis has been made.

Perhaps we may even go a step or two be- yond our deepest expectations and witness the development of a vaccine to be used with our triple or quadruple vaccine in infants, effect- ing the almost absolute prevention of cancer in their lifetime. Perhaps the newer anti- metabolites, known as the fluorinated pyrimi- dines, or some other new chemical compound isolated by purposeful investigation or acci- dentally—as in the case of penicillin—may be the answer to the great problem that besets the physician in his everyday practice. I believe the time has come when we must think in terms of cancer prevention first, rather than cancer detection or treatment. This is the changing responsibility of all physicians, scien- tists and chemists.

Certainly, if about one-tenth of the man- power, money and brain energy used in the past 10 years in devising bombs and satellites had been used for the control and prevention of cancer, this country might very well be the first nation in the world with a vaccine able to destroy or prevent formation of cancer cells.

REFERENCES

1. Frohman, I. P.: The physician as nutritionist. J. Oklahoma M. A. 50:333-340 (July) 1957.
2. ——: Nutrition research in general practice. J. New York M. Coll. 1:9-20 (June) 1959.
3. ——: Tuberculosis survey and the general practi- tioner. M. Ann. District of Columbia 22:133-134; 168 (March) 1953.
4. ——: The role of the private physician in the de- tection of cancer of the lung. Connecticut M. J. 23: 443-446 (July) 1959.
5. ——: The role of the private physician in the de- tection of cancer of the breast. *Ibid.*, pp. 447-449.
6. Saphir, O. and Amronin, G. D.: Obscure axillary lymph-node metastasis in carcinoma of the breast. Cancer 1:238-241 (July) 1948.

Value of Periodic Examinations in Detecting Cancer of the Rectum and Colon

RALPH E. L. HERTZ,* MICHAEL R. DEDDISH† AND EMERSON DAY‡

Memorial Center for Cancer and Allied Diseases, New York

RALPH E. L. HERTZ

THE periodic examination of asymptomatic patients for the detection of cancer is costly in terms of patient and examining-personnel time as well as in monetary outlay. The justification for the widespread use of such a program must depend on two types of evidence: (1) that a significant number of cancers will be detected in these asymptomatic patients and that their chance for cure will be enhanced as compared with patients in whom similar cancers are diagnosed on the basis of symptoms; (2) that premalignant lesions will be discovered and cancers thereby prevented from developing. This report will attempt to shed some light on the first question as it relates to experience with cancer detection in the rectum and colon.

*Consultant, Strang Cancer Prevention Clinic, Memorial Center for Cancer and Allied Diseases, and Assistant Attending Surgeon, Colon and Rectal Service, Memorial Hospital, New York, New York.

†Attending Surgeon, Colon and Rectal Service, Memorial Hospital, New York, New York.

‡Chairman, Department of Preventive Medicine, Memorial Center for Cancer and Allied Diseases, New York, New York.

Study supported by the Falk Fund.

Material

The material to be presented represents the experience of the Strang Cancer Prevention Clinic at Memorial Center in the detection of cancer of the rectum and colon for the years 1946 to 1954. The study period was terminated to permit a five year follow-up at the time of this review. During the interval, 26,126 examinees underwent 47,091 proctosigmoidoscopic examinations. Complete histories and physical examinations as well as additional specific studies were obtained on these patients. Routine periodic proctosigmoidoscopy was performed annually on all patients 45 years of age and over. Guaiac tests for occult blood were done on stools when sufficient material could be obtained at the time of examination. Barium enema studies were performed when either adenomas or intraluminal blood

was seen at sigmoidoscopy and when indicated by symptoms.

It has been the policy of the Strang Clinic to accept only asymptomatic persons for detection study. Nevertheless, cancer of the rectum and colon was diagnosed in seven patients with long-standing histories of severe symptoms, and in eight cases where lesions had been previously diagnosed. This information was withheld at the pre-examination interview for reasons apparent only to the patients. These cases cannot be considered detection material and are excluded from the study. The report will deal with those cases in which cancers were found, although the patients were either asymptomatic or had only minimal symptoms which had not prompted them to seek diagnosis or treatment. It is probable that many of these symptoms, such as blood on the toilet tissue and minimal alterations in the bowel habits, were not related to the presence of the detected cancers.

Carcinoma in an adenoma and carcinoid will be dealt with briefly at the end of this report.

Incidence

Carcinoma was diagnosed in 58 cases to give an over-all detection rate of 0.22 per cent, or one in 450 examinees. The detection rate in women was 0.18 per cent and in men 0.31 per cent. The patients were asymptomatic in 51.6 per cent of cases and had minimal symptoms in 48.4 per cent. The diagnosis was established at the time of the initial visit or on initial proctosigmoidoscopy in 72.3 per cent of patients.

Primary Factors in Diagnosis

The cases were analyzed concerning the primary factor leading to diagnosis and not the method of diagnosis. Thus a patient less than 45 years of age might have been examined with the sigmoidoscope because of the presence of blood on the toilet tissue, and a carcinoma of the rectum found. The symptom of bleeding and not the sigmoidoscopy was the primary factor leading to diagnosis. The finding of an adenoma at routine sigmoidoscopy might have led to a barium enema study, and the diagnosis of a carcinoma of the colon thereby established. Here the primary factor is the sigmoidoscopy. An analysis of the primary factors leading to diagnosis is shown in figure 1.

Routine sigmoidoscopy led to diagnosis in 76.5 per cent of all cases. The tumor was directly visualized in 60.0 per cent. Diagnosis was reached by barium enema studies ordered due to the finding of an adenoma at sigmoidoscopy in 11.5 per cent of cases and of intraluminal blood in 5.0 per cent. Symptoms led to diagnosis in 11.5 per cent of cases, with blood and alteration in bowel habits being of equal frequency. A positive routine guaiac test of the stool was the primary factor in 8.0 per cent, and anemia in 3.5 per cent. Digital rectal examination was positive in only 9.5 per cent of cases.

Distribution

Multiple carcinomas were found in four of the 58 cases, to give a total of 62 lesions. It is of interest to note that 59.2 per cent of these tumors were encompassed within the sigmoidoscopic field. This figure closely approximates the general experience of autopsy series and of surgical reports. This would appear to suggest that the detection methods used offered excellent performance above the range of the sigmoidoscope. This is not entirely true as lesions will be missed if barium enemas are not routinely performed. It has not seemed feasible to introduce them as an over-all routine. A breakdown of the distribution of these lesions within the large intestine is presented in figure 2. The distribution within the sigmoidoscopic field is presented as those above and those below 10 cm. from the anal verge.

Staging

The patients diagnosed at the Strang Clinic received definitive treatment at different hospitals. Adequate information for grouping according to the classification by Duke was not always available. However, there was a statement concerning the presence or absence of node metastases in all but six instances. All cases were operable and there were only two palliative resections to give a resectable-for-

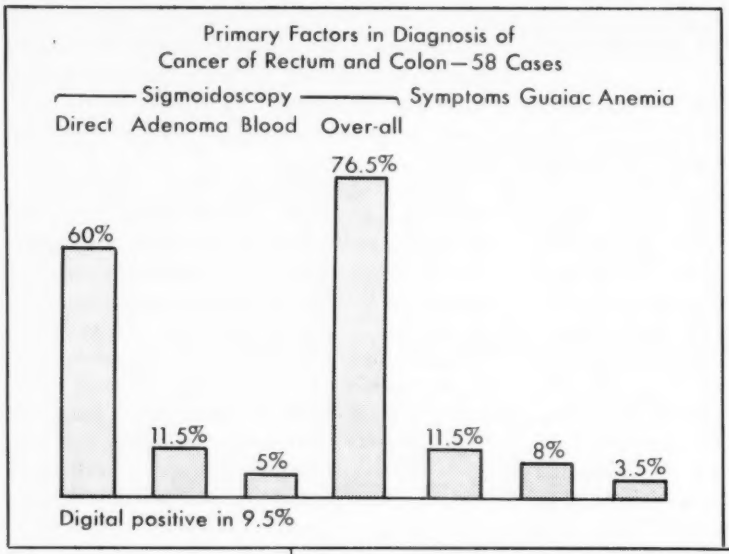


FIGURE 1.

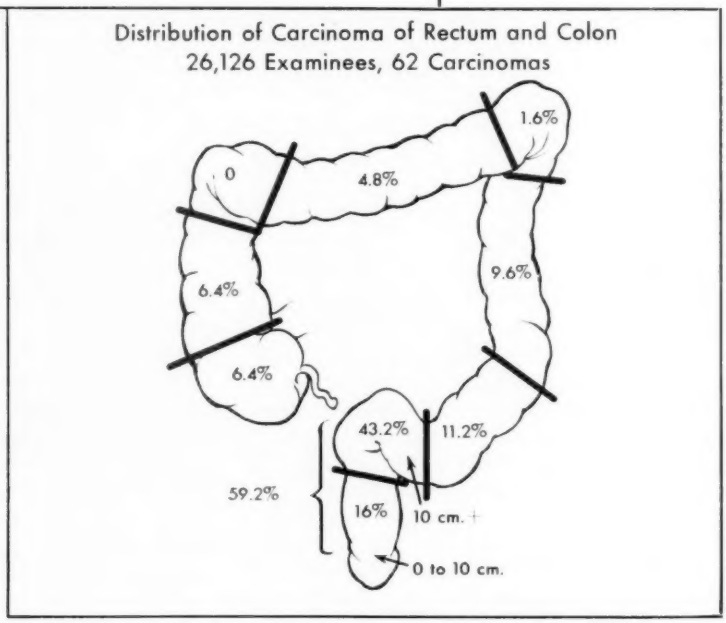


FIGURE 2.

cure rate of 96 per cent. The staging of these cases is presented in figure 3. The patients are grouped according to Duke's classification, except that 17.3 per cent are considered Duke's AB, as the only information available was that they were node-negative patients. The incidence of resected cases without evidence of node metastases was 80.6 per cent.

Survival Experience

The study was terminated to permit a five year follow-up at the time of review. It was felt necessary to present the entire experience of this block of consecutive examinations. Some patients delayed in carrying out final diagnostic measures or in seeking treatment

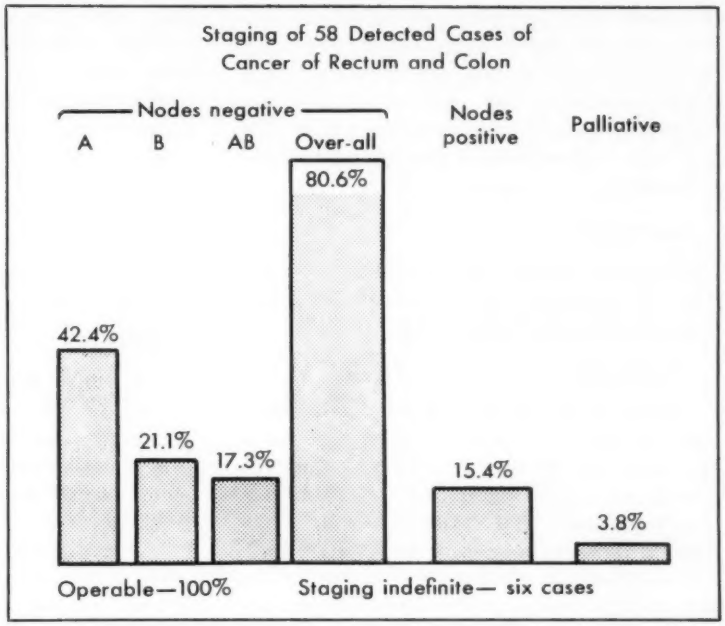


FIGURE 3.

or both, so that three patients were not yet five years postoperative. A follow-up to at least five years or to the maximum possible period was obtained in 94.7 per cent. This experience is presented in table 1.

It will be noted that no follow-up was obtained in three patients and that three patients were alive without evidence of disease at less than five years. Two patients died from other causes without evidence of disease. This left 50 determinate patients of whom 44 survived five years for an over-all survival rate in the determinate cases of 88 per cent.

Cancer Arising in Adenomas

Cancer was found in four asymptomatic patients at sites where the diagnosis of an adenoma had previously been made. In each of these instances the advice for excision of these lesions had been ignored, and the patients had returned for re-examination at intervals ranging from 4 to 13 years. Initial biopsy of the adenoma was obtained in only two instances. In one of them, biopsy was performed on a pedunculated adenoma, and the patient returned after 13 years with an annular Duke A lesion at the same level. In the second case, biopsy was performed on a partially pedunculated adenoma. The patient returned in four years with a 3.0 cm. Duke A carcinoma at this site. Multiple sections failed to reveal residual adenoma.

Carcinoma in an Adenoma

Carcinoma in an adenoma is here considered to include lesions which present *in situ* or early infiltrative carcinoma in an adenoma. These lesions have not been included in the previous discussion of cancer. Carcinoma in an adenoma was found in 47 cases, or 0.18

TABLE 1

FIVE YEAR SURVIVAL IN DETECTED CANCER OF RECTUM AND COLON

Number of cases		58
Determinate	50	
No follow-up	3	
Alive without evidence of cancer 45, 56 and 59 months	3	
Died of other cause without evidence of cancer	2	
Five year survivors		44 (88%)

per cent. The detection rate in women was 0.16 per cent and in men 0.22 per cent. Sigmoidoscopy was the primary factor leading to diagnosis in 92.4 per cent. The tumor was directly visualized by sigmoidoscopy in 75.6 per cent. Approximately three-fourths of the patients were asymptomatic.

Carcinoid

Carcinoid tumors were found in 0.06 per cent of examinees. They were all small and clinically benign lesions.

Discussion

Cancer of the rectum and colon is the most common type to affect man when both sexes are combined. Management of this problem is therefore a central one in cancer control. This review indicates that a worthwhile detection rate for these lesions can be achieved by periodic examination and that when lesions are so detected, patients can be offered a greatly enhanced chance of surviving their disease. The practice of routine sigmoidoscopy on a well-prepared bowel is the essential feature of this examination, representing the primary factor in diagnosis in 76.5 per cent of cases. The technic of sigmoidoscopy does not belong to the specialist alone but must be a part of the armamentarium of all physicians interested in cancer detection. The significance of the digital rectal examination in the detection of cancer of the rectum and colon has been highly overrated. In this series, only 9.5 per cent were so diagnosed even though the patients were examined after bowel preparation. It is noteworthy that 40.0 per cent of the lesions detected were beyond the reach of the sigmoidoscope. Nevertheless, some colonic cancers were undoubtedly missed.

A review of cancer detection in 15,648 men and women on initial examination in the Strang Clinic for the years 1954 through 1955 showed 29.5 per cent of lesions to be within the rectum and colon, if the skin is excluded. The rate is approximately 20.0 per cent of all detected cases in women, and 60.0 per cent in men. The rate for women should be somewhat higher, as many cancers at other sites were diagnosed in women below the age of 45, and those within this age group were not sigmoidoscoped. The diagnosis of three-fourths of these cases is attributable to sigmoidoscopy. This discussion has given no cognizance to the importance of the detection of adenomas in cancer prevention, although it may be a more important contribution than the early detection of cancer. These facts cannot but impress one with the necessity of incorporating sigmoidoscopy as an integral part of any cancer detection program.

Summary

1. Periodic proctosigmoidoscopic examination produced a cancer detection rate of 0.22 per cent, or one in every 450 examinees.

2. Proctosigmoidoscopy was the primary factor leading to diagnosis in 76.5 per cent of cases.

3. The diagnosis of carcinoma was established at the time of initial visit or on initial proctosigmoidoscopy in 73 per cent of cases.

4. These cases of detected cancer would appear to represent early cancer, as evidenced by an operability rate of 100 per cent, a resectable-for-cure rate of 96 per cent, and an over-all five year survival rate of 88 per cent. This impression is further supported by the low incidence of lymph node metastases.

5. Two cases are presented in which carcinomas appear to have arisen in previously benign adenomas after an observation lapse of four and 13 years.

6. Carcinoma in an adenoma was found in 0.18 per cent of examinees.

7. Carcinoid tumors were found in 0.06 per cent of cases.

Conclusion

Based on these results, one must conclude that periodic examination did detect a significant number of cancers of the rectum and colon. Sigmoidoscopy was by far the most important single phase of the examination. The patients in whom cancers were found on detection examination were offered a greatly enhanced chance of surviving the disease as compared with patients in whom diagnosis is reached at later stages because of the presence of symptoms.

Value of Periodic Examination in Head and Neck Cancer

GRANTLEY WALDER TAYLOR*

Massachusetts General Hospital, Boston

GRANTLEY WALDER TAYLOR

MOST cancers of the head and neck occur in areas subject to direct and frequent observation by the patient himself or his immediate associates. Nowhere is the efficacy of self-examination better exemplified than in those areas which a person inspects daily before a mirror while brushing his hair, shaving, or applying cosmetics.

Lesions involving the skin are noted in this way in almost all cases, and those not found directly by the patient are drawn to his attention by his associates. Not only are new lesions noted in this way, but changes in pre-existing lesions are also promptly apparent.

It is undoubtedly for these reasons that most skin carcinomas of the head and neck are of very small size when first brought to the attention of a physician and are so readily curable. Similarly, malignant melanomas in these areas are smaller and of shorter duration than those elsewhere on the body and carry a more favorable prognosis. Dr. Shields Warren years ago called attention to the earlier diagnosis, smaller size and more favorable prognosis of cancers situated on all exposed parts of the body.

Not only are the local lesions more curable when they are small, but also there is a lower incidence of regional node metastasis from the small and early cancers. Radical measures of eradication are more readily accepted by the patient when extensive mutilating procedures can be avoided.

Similar findings also apply to carcinoma of the lip where observation and comments of others focus attention on the lesion and demand appropriate treatment.

Self-inspection and examination also play a prominent role in detection of early cancers within the mouth. Direct visual inspection by the patient and the constant check on intraoral areas by the patient's tongue reveal irregularities and early lesions in a large number of cases. Such early lesions may be noted because they impart a bad color to the breath on which sometimes the patient's associates will comment.

Examination of the mouth is also a routine procedure of all dentists, and a large number

*Board of Consultation, Massachusetts General Hospital, Boston, Massachusetts.

of early and asymptomatic lesions are found in this way. An increasing number of patients are accustomed to accept routine periodic checkup examinations by their dentists, who are more and more alert to institute or advise investigation of cancerous or precancerous lesions which they encounter during these examinations.

Doctors are often negligent in their routine examinations of the mouth, being content with a quick look at the palate and tonsils with the help of a tongue depressor and having the patient stick out his tongue. Such a perfunctory examination will overlook most early carcinomas and precancerous lesions.

Provided that a careful survey is made, periodic examinations may be expected to discover cancer or precancer in a stage when the lesion is early and small and when measures of eradication may be curative without causing extensive mutilation. The cancers of small size and brief duration are much less likely to present lymph node metastases and, as a result, offer a much higher likelihood of cure. In studies made some years ago, small cancers of short duration were associated with metastases in only a few cases; in contrast, the large lesions of longer duration had a high incidence of metastases as well as a much lower rate of cure.

Periodic examinations of the asymptomatic patient may be expected to find tumors of the salivary glands and thyroid gland in an early stage. Again, at this stage the prospect for cure is much brighter.

The routine periodic physical examination itself will rarely disclose early cancer of the pharynx, larynx, accessory sinuses or esophagus. On the other hand, careful questioning in regard to apparently trivial symptoms, such as nasal discharge, swallowing difficulty or hoarseness, should excite suspicion enough to warrant roentgenographic studies, laryngoscopy and other diagnostic procedures.

The discovery of asymptomatic masses in the neck may lead to studies to establish diagnoses of lymphoma or sarcoma, or metastatic carcinoma which is secondary to an occult primary focus.

In summary, a periodic examination with careful interrogation, inspection and palpation should discover a very high percentage of cancers in the head and neck area which are in an early stage and favorable for cure.

Value of Periodic Examination in Early Cancer of the Breast

EDWARD F. LEWISON*

The Johns Hopkins University School of Medicine, Baltimore

EDWARD F. LEWISON

THE value of periodic examination—and by this procedure I mean a physical examination by a physician at periodic intervals supplemented by self-examination by the patient as a regular monthly routine—rests on the cardinal concept that cancer of the breast is more readily "curable" if diagnosed "early." However, with this particular malignancy the term "early" must be carefully defined as it may mean many things to many men. Steiner has suggested that early cancer in the clinical sense is mainly temporal and means the recent onset of signs or symptoms; in the histologic sense early may mean being preinvasive; in the anatomic sense early breast cancer signifies a tumor which is small and still freely movable without evidence of cancer cells circulating in the blood stream; in the therapeutic sense it denotes a well-localized lesion which is amenable to complete surgical excision or successful radiotherapy; in the prognostic sense it indicates a favorable chance of cure, and in the biologic sense it implies recency or newness in its natural history—which I suppose may be considered by some to be the precursor of predeterminism. Thus, the earliness of breast cancer cannot be measured merely in minutes or months but must be measured by many meanings, some of which represent the broad and comprehensive manifestations of malignancy and metastasis.

If periodic examinations are to be valuable, they *should be* successful in detecting breast cancer early in its clinical sense; they *can be* successful in detecting breast cancer early in its anatomic and biologic sense; but they *must be* successful in detecting breast cancer early in its therapeutic and prognostic sense. For there is a great advantage in extolling the virtue of periodic examinations if we can claim that by this procedure breast cancer *is* more readily "curable."

Among the pertinent problems posed by this symposium is the premise that periodic examinations actually are of value. Is it true that the benefits of this procedure are real and not wishful or imaginary? Can the precept for periodic examination be merely a prover-

*Assistant Professor of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

bial platitude the strength of which lies in our own diagnostic weakness? What are the validity and the verification for this type of cancer vigilance?

There is ample clinical evidence to indicate that in the breast, which is the most common single site of malignancy in women, cancer early in time and early in size is more apt to be curable. In this country the excellent educational efforts of the American Cancer Society have resulted in a general public alert (if not actual apprehension) to the danger sign of a lump in the breast. For the breast is an accessible surface organ which can readily be examined by the patient, her husband and her doctor. Thus, the opportunity for the early recognition of an unusual thickening or lump in the breast should be exceptionally good.

From an extensive medical and surgical literature one can find a very close correlation between the duration of the disease (the so-called waiting period or delay) and its stage or advancement. This in turn is generally reflected in prognosis and survival rate—the shorter the time, the longer the survival. Whereas the duration of the disease may be an accurate expression of tumor growth and host resistance, the reliability of the time factor which is so dependent on the personal human equation must be interpreted with considerable caution. I believe that almost all patients have a tendency to tamper with the truth of time in accord with either their hopes or fears.

Our own statistics indicate that the most favorable prognosis is present in patients with breast tumors of *short duration*, but a surprising number of patients with a long clinical history survive the five year period. Perhaps the patients with more aggressive tumors were readily recognized and promptly treated, whereas the slow-growing lesions were less likely to be discovered early, and by virtue of their natural indolence enabled the patients to survive a long period of time. Shimkin, for instance, has shown that the average patient survives 45 months when there has been less than one month of delay, whereas the average patient survives 66 months if there has been more than 36 months of delay. Certainly this cannot be construed to mean that delay is desirable. On the contrary it must mean that biologic selectivity is of considerable importance in the matter of survival.

In the Netherlands, Wassink conducted a careful clinical analysis of breast cancer and found a rather remarkable decrease in the over-all duration of the disease during the last half century. There was a gradual but important improvement in the quality of operable patients which could "only be ascribed to a reduction in the 'waiting time'." Since there were no convincing reasons for attributing this to altered patient selection, it must be regarded as the favorable effect of cancer education and a desire to seek medical examination at an earlier time.

At The Johns Hopkins Hospital during the period 1935 to 1945 we found quite uniformly that only one-third of the patients with operable breast cancer had a stage I disease—no pathologic evidence of axillary metastases—at the time of surgery. However, in our more recent tumor registry statistics there can be noted a definite improvement. In the years 1954, 1955 and 1956 the proportion of patients without axillary metastases—stage I disease—had increased to 43 per cent, 45 per cent and 42 per cent, respectively. This is indeed encouraging and may very well be the tangible result of earlier detection, diagnosis and treatment.

In a recent review of the clinical material at New York Memorial Hospital, Robbins and Bross found that in patients who delayed their treatment less than one month, 45 per cent were early in that they had no axillary metastases, whereas in those patients who delayed their treatment more than 12 months, only 25 per cent were still early, or free of axillary metastases. Thus, in this matter of delay, procrastination may be more deadly than a mere killer of time; for the problem of prognosis is perplexing, but chance, inscrutable and unpredictable, is most often on the side of the prudent.

It is considered almost axiomatic among some surgeons in predicting prognosis that the smaller the breast tumor, the better the end result. Our own statistics on this subject indi-

TABLE 1

END RESULTS OF RADICAL MASTECTOMY IN PATIENTS WITH PRIMARY BREAST CANCER

STAGE OF DISEASE	NUMBER OF PATIENTS	FIVE YEAR SURVIVAL	
		Number	*Per cent*
Localized	59	42	71
Regional	126	43	34
Distant	0	0	0
Total	185	85	46

cated that in stage I breast cancer the five year survival rate for patients with small tumors (less than 2.5 cm. in diameter) was 74 per cent, whereas for patients with large tumors (more than 5.0 cm. in diameter) it was only 53 per cent, treatment being the same. A similar striking difference was noted for patients with a more advanced stage II disease. Robbins and Bross reported "far more patients with small lesions, regardless of axillary node involvement, are alive five years after radical mastectomy than are patients with larger lesions. . . ." Haagensen and Stout noted that "the prognosis gets worse as the size of the tumor increases." Their data denote a 62 per cent clinical "cure" rate for breast tumors smaller than 3 cm. and only a 20 per cent clinical "cure" rate for breast tumors larger than 6 cm. Thus, although tumor size alone cannot be regarded as an infallible index of prognosis, it is certainly a very suggestive straw in a wistful wind.

There is almost unanimous agreement that the most important measurable factor in the prognosis of patients with breast cancer is the presence and extent of axillary metastases. This single factor alone is the most significant and reliable prophet of prognosis. In our own series of patients treated rather uniformly by means of radical mastectomy, the five year end results revealed a 71 per cent survival rate for patients *without* axillary metastases and only a 34 per cent survival rate for the patients *with* axillary metastases present (tables 1 and 2).

At the Memorial Center the five year survival rate for patients with a small tumor (less than 2 cm. in size) and an early lesion (less than two months' duration) was 95 per cent when no axillary nodes were involved, 67 per cent when the lower level axillary nodes were involved, and 50 per cent when the highest level axillary nodes were involved. A similar situation prevailed in the cases of large tumors of long duration. This suggests that breast cancer progresses from one axillary node level to the next and that the extent of these metastases is a reliable measure of the spread of the disease. Thus, both the stage and the advancement of the tumor are of paramount importance in predicting prognosis.

The current cancer education programs sponsored by the American Cancer Society have resulted in a great increase in interest in periodic health examinations. However, these physical examinations alone, valuable as they are, performed annually or even once every six months, cannot be the entire bulwark of public defense against cancer. If breast cancer is to be detected early, it is the duty of every

TABLE 2

END RESULTS IN 259 PATIENTS WITH PRIMARY BREAST CANCER

STAGE OF DISEASE	NUMBER OF PATIENTS	SURVIVAL			
		5 YEARS		10 YEARS	
		Number	*Per cent*	*Number*	*Per cent*
Localized	71	49	69	35	49
Regional	156	46	30	25	16
Distant	30	0	0	0	0
Unknown	2	0	0	0	0

woman herself to recognize the danger signals and practice breast self-examination as a regular monthly health habit. Several years ago we had the opportunity of testing the effectiveness of teaching this technic to a very large group of women working for the Social Security Agency. Briefly, our results indicated that a large number of the women who saw the film "Breast Self-Examination" and participated in the discussion became quite breast conscious. During a six month follow-up period, there were 569 women, or 24 per cent of this group, who went to see their doctors for more complete and thorough examination of their breasts. Three women in this group were operated on for breast cancer, which is three times the expected incidence of breast cancer over this period of time. Perhaps it is the hope that springs eternal that leads us to believe that these three women discovered their breast cancers early, in the very best sense of the word. Time alone will tell the true value of breast self-examination, but I believe that in these three patients the prognosis is probably good. May long life and "joy cometh with the morrow."

Thus, almost 2000 years ago, Celsus said that "only the beginnings of a cancer permit of a cure" and today our therapeutic efforts are still founded on this tenet. Breast cancer is "curable" if the diagnosis is early, the tumor is accessible, and the size is small. The effect of more recent cytologic studies concerning cancer cells circulating in the blood stream certainly will have an important bearing on this concept. However, it must be remembered that the average survival span for patients with *untreated* breast cancer is about three years; for all patients with *treated* breast cancer about five years; and for those cases in which the cancer is detected in time and treated early, about 13 years.

Like all maxims which are tempting in theory but thorny in practice, the precept that periodic examinations are valuable in the detection of early cancer of the breast must be regarded as imperative for the public but imperfect for the patient. For I am sure that all of us can recall an individual patient who has been operated on at the earliest possible time with a lesion that was barely discernible, only to find that metastases had already cast their shadows before them. It must be clearly recognized that in some patients even the most faithful and careful periodic examinations will fail to find early breast cancer. In those patients with lesions of long mitotic intervals every effort must be made to advance the date of the detection of their disease by methods yet to be discovered.

In my own suburban community outside of Baltimore there recently appeared a newspaper notice which read: "The voluntary fire department will blow the siren 15 minutes *before* the start of each fire." While awaiting the sanguine prospect of such a siren—and I cherish the hope that a predictive warning test for cancer is not beyond expectation—all of us must become "more and more alert to the dangers of breast cancer on less and less clinical evidence." By promoting the practice of periodic examinations we may be able to detect those silent and asymptomatic cancers before they have disseminated their disease beyond us. However, that which is gained by the patient's self-examination must not be lost by the physician's procrastination or watchful waiting. In educating the public, as well as the profession, in cancer control, we must encourage them to perform this simple health habit carefully, routinely and with a high index of suspicion. In this way, I sincerely believe that we can discover today what would be all too obvious tomorrow!

Value of Periodic Examinations in Detecting Cancer of the Genitourinary System

ROGER BAKER*

Georgetown University School of Medicine, Washington, D.C.

ROGER BAKER

By and large, the scope and limitations of radical surgery and the use of irradiation in treating genitourinary cancer have been defined. The cure rates achieved by these therapeutic modalities have leveled off and have just about reached a plateau. Improvement of current statistics must be found in other areas such as earlier recognition and treatment. It is impossible at this time to prove that periodic examination of the genitourinary system would result in earlier detection and increased cure rate of genitourinary cancers. The difference between curable and incurable cancer, however, is the difference between detection and treatment in time as compared with detection and treatment too late for cure. In essence, the significant factor is one of time. Applying this basic concept, it is reasonable to assume, therefore, that periodic examination should provide earlier detection and treatment and improved cure rate of genitourinary cancers.

While the need for periodic examinations of the genitourinary system is reasonable, it is also reasonable that the family physician cannot refer to a urologist each and every one of his patients for that examination. It is not practical or necessary that he do so, provided he is willing to accept certain elementary urologic concepts. It is important to remember that if the genitourinary examination is performed correctly, the results obtained by the family physician can be identical to those of the specialist in urology. In addition, the procedures and methods used are identical to those used by the specialist for periodic examination. Finally, the cost to the patient for periodic genitourinary examination is no more than that of an office visit which includes simple history, simple physical examination, and routine urinalysis.

Regardless of these very favorable factors concerned with examination of the genito-

*Professor and Director, Division of Urology, Georgetown University School of Medicine, Washington, D.C.

urinary system, there has been little effect to date on earlier detection of these cancers. The classic example is that noted in patients with prostatic carcinoma. Approximately 95 per cent of such patients continue to be referred to the urologist when the lesion has already metastasized. This unfortunate situation is the result of several conditions: (1) the silent nature of certain cancers; e.g., not all bladder cancers produce hematuria; (2) lack of regular periodic examinations; e.g., it is impossible to detect early carcinomas if patients do not appear for examination; (3) incomplete or incorrectly performed examinations; e.g., it is impossible to detect early carcinoma of the prostate if all the characteristics of the early lesion are not known; (4) failure of the examining physician to appreciate the gravity of certain signs and symptoms; e.g., microscopic hematuria is fully as significant as gross hematuria in the diagnosis of renal or bladder carcinoma.

In an effort to reduce to a minimum these possible mistakes, this paper presents certain aspects of periodic examination of the genitourinary system which ordinarily require more attention than the routine.

Kidney and Bladder

Over 23,000 patients died last year from cancer of the genitourinary system. This represents 16 per cent of all cancer deaths and is exclusive of the female genital system malignancies. A large percentage of these deaths were due to carcinoma of the kidney and bladder. The single most frequent finding in such patients is hematuria, either gross or microscopic. For some reason it is impossible to impress on certain physicians that in cases of renal or bladder carcinoma there may be only microscopic hematuria. Persistent microscopic hematuria from a renal or bladder cancer has just as deadly an implication as gross hematuria. If routine examination of a patient over 30 years of age reveals, on repeat examination, an abnormal number of red blood cells in the centrifuged urinary sediment, urologic investigation is mandatory.

At present, most persons do not have periodic examinations; hence, when a lesion of the kidney or bladder is present, it is only when gross hematuria finally appears that patients rapidly consult their physicians. As most such lesions produce gross hematuria only when far advanced, the cure rate of such treatment is lower than might reasonably be expected.

Another point that is difficult for urologists to impress on their nonurologist medical confreres is that renal and bladder cancers have a remarkable tendency to cause bleeding which stops spontaneously. In such instances the patient usually consults the physician, and oftentimes it is the physician who is reluctant to insist on urologic study, as the gross hematuria has ceased. If necessary, it is suggested that the possible differential diagnosis of gross hematuria be explained to the patient. It is far better to have a complete urologic workup of 25 consecutive cases of hemorrhagic cystitis than to overlook one patient with cancer of the kidney or bladder because urologic investigation was not insisted on.

The last patient I treated for cancer of the kidney had intermittent gross hematuria for 12 months before being referred for urologic investigation. Dr. William Taylor of Ohio State University School of Medicine found that 23 of 25 patients with renal cancer had blood in the urine for an average of 21 months before the diagnosis was made. These facts speak for themselves and further elaboration is not necessary.

There are specific key signs other than microscopic or gross hematuria that may be misleading and obscure the diagnosis of renal or bladder neoplasms at the time of a periodic examination:

Kidney tumors—Wilms' (nephroblastoma) tumor of children is usually characterized by a palpable mass rather than pain or hematuria. Some 25 to 50 per cent of such children have hypertension and about one-half also have fever. Approximately 50 per cent of adult patients with carcinoma of the renal pelvis may have a dull costovertebral ache rather than the classically accepted sharp pain. Of patients with hypernephroma, only about one-fifth will have a palpable abdominal mass. As a consequence the abdominal findings in hy-

pernephroma are not as significant as formerly taught. While slightly over one-half of these patients will have pain in the costovertebral angle, it is usually a dull ache. About one out of five patients with hypernephroma will have an unexplained temperature elevation. Many patients with a renal tumor of any type will have vague gastrointestinal disturbances.

Exfoliative cellular cytology should not be an office procedure for patients suspected of having a renal tumor. If there are sufficient suspicious symptoms to justify its use, there are sufficient indications for urologic workup. The results of cystoscopy and retrograde pyelography are so effective that use of the Papanicolaou smear technic by urologists is unnecessary except in very rare circumstances.

Bladder tumors—These tumors are second in frequency only to carcinoma of the prostate as a cause of genitourinary deaths.

At the time of periodic examination, patients should be questioned concerning any past history of bladder papilloma. Papillomas of the bladder have a marked tendency to recur and such recurrences are often malignant. These patients require regular cystoscopic examination of the bladder.

Bladder carcinomas are often secondarily infected, and hence the presenting signs or symptoms may be those of the associated recurrent cystitis. Within the past year I have seen two patients with metastatic carcinoma of the bladder who had been under careful treatment by their family physicians for recurrent low-grade cystitis for periods of six and nine months, respectively, prior to referral for urologic investigation.

Sometimes it may be necessary to obtain an intravenous pyelogram after periodic examination. Too much importance cannot be placed on the "normal intravenous pyelogram." It should be remembered that bladder tumors are not well visualized at the time of intravenous pyelography.

Concerning Papanicolaou smear technic for urinary sediment in a suspected case of bladder cancer, the situation can be summarized as follows: If there is enough suspicion to perform the Papanicolaou test, cystoscopy is necessary and gives far more reliable information.

Testis

Approximately 700 men die each year from cancer of the testis and about one-half of this number are between the ages of 20 and 40 years. In fact, 13 per cent of cancer deaths of men in this age range are due to testicular cancer. Treatment of this lesion by surgery or irradiation or both has been gratifying, but the cure rate is no longer improving. Improvement of the existing cure rate is certainly possible by earlier detection of such lesions. One area of this problem that deserves further discussion is that of the cryptorchid testis.

Of patients with cancer of the testis 10 per cent have cryptorchism, and the cancer is in the cryptorchid testis. The cryptorchid testis and the atrophic testis are approximately 50 times more prone to malignancy than chance association or than the normal testis. This fact has an interesting aspect. The incidence of cancer in the normally located testis is two per 100,000 population. In cryptorchism, however, the incidence is about 100 per 100,000, or almost as frequent as carcinoma of the prostate.

These data can be approached from another standpoint. Ten per cent of all patients with cancer of the testis have cryptorchism and 700 men die each year from this disease. It can be reasonably stated, therefore, that about 70 deaths could be prevented if the cryptorchid testis were excised before the development of cancer. It would thus appear that all unilateral cryptorchid testes in postpuberal males should be removed. The subject is open to controversy, however, among urologists.

Some urologists suggest performing orchiopexy on the postpuberal patient in order that the cryptorchid testis may be readily palpated. The evidence indicates, however, that changing the location of the cryptorchid testis has no effect whatever on its premalignant potential. Furthermore, if orchiopexy is performed, there is no assurance that such patients will continue to return on an indefinite basis in order to have their testes palpated for the development of nodule. Should such patients be faithful in returning for three or four examinations each year for the next 10 or 20 years

(which is unlikely) and should a nodule become palpable, the lesion may already have metastasized. If the nodule represents a chorioepithelioma, the mortality rate is about 100 per cent. Finally, there is a small percentage of patients with cancer of the testis in whom the lesion cannot be palpated even at surgery.

As a result of all this reasoning, most urologists either perform orchiectomy for the postpuberal cryptorchid testis or do nothing. Those urologists who do not excise such unilateral testes justify their stand with the statement that cancer of the testis is a very rare condition, as only 700 men per year die of the disease. A large number of the patients with unilateral cryptorchism would require surgery in order to prevent cancer in only 70 patients. Urologists on the opposite side claim that the mortality rate from orchiectomy is almost nonexistent, and hence they perform such surgery in an attempt to salvage these same 70 patients.

So the controversy goes. It is presented in brief here so that at the time of periodic examination it can be appreciated that the adult male with unilateral cryptorchism has no signs and symptoms, yet there is potential danger. These patients present a problem that should be discussed with the urologist.

The patient with either hydrocele or epididymitis diagnosed at the time of periodic examination deserves special mention. Any acquired hydrocele of the testis should be considered suspicious as possibly masking a testis carcinoma. About 10 per cent of testis cancers have a hydrocele. Urologists either surgically explore acquired hydroceles or tap the hydrocele sac. Withdrawing the fluid from the hydrocele sac is not done in an attempt to cure the hydrocele, but to afford easier palpation of the testis. It is unfortunate that about 25 per cent of the patients with testis carcinoma referred to urologists have been diagnosed and treated earlier for hydrocele or epididymitis.

Prostate

Approximately 12,000 men die each year from prostatic carcinoma, yet in about 90 per cent of the patients this malignancy begins in the area of the prostate that is palpated at the time of rectal examination. Strangely enough, only 5 to 10 per cent of the patients with carcinoma of the prostate are referred to the urologist early enough so that radical surgery can be attempted. There are two possible reasons for this: Not enough periodic examinations are done on men over the age of 45 years, and physicians are not completely familiar with the digital characteristics of early carcinoma of the prostate.

In performing rectal examination of the prostate, not only is the size of the gland of interest, but more important is the presence or absence of a localized area of nodularity or increased density. These lesions are nontender. There does not have to be a palpable nodule raised above the surface of the gland in order for early carcinoma to be present. The centimeter-sized area of increased density within the gland may well represent a cancer. Neither the nodule nor the localized area of increased density need be as firm as a stone, but simply firmer than the adjacent gland.

Any nodule or area of increased density in the prostate gland of a man over 45 years of age is cancer until proved otherwise. To ignore this elementary principle is often disastrous. In order to obtain proof of diagnosis the next step is biopsy of the suspicious area. Exfoliative cellular cytologic studies on urine or the prostatic secretion have not been too effective. The early lesions are situated too far posteriorly in the gland to exfoliate malignant cells into the urethra for efficient detection when it is most needed.

Biopsy is performed by either needle or open perineal excision of the nodule for frozen section. If the needle biopsy is positive for cancer, surgery is indicated. If the needle biopsy is negative, a persistent doubt remains, and surgery is usually indicated to permit excision of the nodule for confirmatory microscopic data. Perineal needle biopsy often gives a misleading negative result in the early stages of the disease. As a consequence, this fallibility of needle biopsy has prompted many urologists to abandon it and resort to perineal exposure of the prostate with excision of the entire nodule for frozen section.

As previously stated, only about 5 to 10 per cent of patients with prostatic carcinoma

are seen sufficiently early to justify radical prostatectomy. The remaining 90 to 95 per cent of patients with this disease already have proved metastatic carcinoma. The value of periodic examination of the prostate has been strikingly pointed up in papers reported by the Medical Department of the Armed Forces, where an obligatory yearly examination of their personnel is performed. Kimbrough[1] reported that of the patients with prostatic carcinoma admitted to the Walter Reed Army Hospital 56 per cent were treated by radical operation; only 44 per cent were too far advanced for curative surgery. While Kimbrough's cure rate of patients treated by radical prostatectomy was no greater than that of his civilian counterparts, regular periodic examination afforded an opportunity for earlier diagnosis and treatment.

Conclusion

Periodic genitourinary examinations are worth the effort and require no specialized or expensive procedures other than the standard history, physical examination and urinalysis. If the genitourinary examination is performed correctly, with proper emphasis placed on the findings obtained, the results of such examinations can be identical to those of the specialist in urology. Various aspects of carcinomas of the kidney, bladder, testis and prostate that require special consideration have been presented in this discussion.

REFERENCE

1. Kimbrough, J. C.: Carcinoma of the prostate. Five year follow-up of patients treated by radical surgery. J. Urol. 76:287-291 (September) 1956.

Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-160; additional listings are on page 415.

Modern Surgical Monographs. Open Reduction of Common Fractures. By Oscar P. Hampton, Jr., M.D., Assistant Professor of Clinical Orthopedic Surgery, Washington University School of Medicine, St. Louis, and William T. Fitts, Jr., M.D., Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia. Vol. 1. No. 2. 212 pages with 72 illustrations. 1959, Grune & Stratton, Inc., New York and London. $8.75. $23.00 for series.

Mitral Valvulotomy. By Harold J. Stewart, M.D., Professor of Clinical Medicine, and Frank Glenn, M.D., Lewis Atterbury Stimson Professor of Surgery (Chairman), Cornell University Medical College, New York. 244 pages with 25 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $10.50.

The Preparation of Medical Literature. By Louise Montgomery Cross, M.A. 451 pages with 80 illustrations. 1959, J. B. Lippincott Company, Philadelphia and Montreal. $10.00.

Neurology. By Roy R. Grinker, M.D., Director, Institute for Psychosomatic and Psychiatric Research and Training, Chicago, Paul C. Bucy, M.D., Professor of Surgery, Northwestern University School of Medicine, Chicago, and Adolph L. Sahs, M.D., Professor, Department of Neurology, State University of Iowa College of Medicine, Iowa City. Ed. 5. 1,386 pages with 445 illustrations. 1960, Charles C Thomas, Springfield, Illinois. $24.50.

Night Vision. By Gaetan E. Jayle, M.D., Professor of Clinical Ophthalmology, Albert G. Ourgaud, M.D., Professor of Ophthalmology, Faculty of Medicine of Marseilles, France, L. F. Baisinger, M.D., Ophthalmologist, Bakersfield, California, and William John Holmes, M.D., Ophthalmologist, Honolulu. 408 pages with 181 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $13.50.

Symposium on Glaucoma. Transactions of the New Orleans Academy of Ophthalmology, 1957. Edited by William B. Clark, M.D., Professor of Clinical Ophthalmology, Tulane University School of Medicine, New Orleans, with eight contributors. 314 pages with 99 illustrations. 1959, The C. V. Mosby Company, St. Louis. $13.50.

Cutaneous Manifestations of the Malignant Lymphomas. By Samuel M. Bluefarb, M.D., Associate Professor of Dermatology, Northwestern University Medical School, Chicago. 534 pages with 47 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $15.50.

The Fluids of Parenteral Body Cavities. Modern Medical Monographs. By Paul D. Hoeprich, M.D., Assistant Professor of Medicine, and John R. Ward, M.D., Assistant Professor of Medicine, University of Utah College of Medicine, Salt Lake City. No. 19. 98 pages with 11 illustrations. 1959, Grune & Stratton, Inc., New York and London. $4.75.

Christopher's Minor Surgery. Edited by Alton Ochsner, M.D., Professor of Clinical Surgery, Tulane University School of Medicine, New Orleans, and Michael E. DeBakey, M.D., Professor of Surgery, Baylor University College of Medicine, Houston, with 24 contributors. Ed. 8. 539 pages with 347 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $10.50.

Early Diagnosis of Cancer of the Gastrointestinal Tract

DONALD B. SHAHON* AND OWEN H. WANGENSTEEN†

University of Minnesota Medical School, Minneapolis

DONALD B. SHAHON

IT is obvious to those engaged in the treatment of neoplastic disease that there is a group of patients who, regardless of how early their cancer is diagnosed and properly treated, nevertheless succumb to the disease. However, it is equally apparent to physicians engaged in the treatment of cancer that if therapy is instituted when the neoplasm is still within the local confines of the parent organ, the chance for cure is from two and one-half to four times greater than when the disease has extended even to a single regional lymph node. When the diagnosis of cancer is made as a result of symptoms or obvious signs of disease, approximately 60 per cent of these patients will be dead within five years after the diagnosis is made. Only 30 per cent of patients with major forms of cancer have a localized lesion at the time of diagnosis. In about 50 per cent of patients, unfortunately, the cancer is beyond the bounds of present-day cure or remedial agents when the diagnosis is first established.[1]

The aforementioned facts paint a gloomy picture of the entire problem. However, from the experience obtained from an 11 year study at the University of Minnesota Cancer Detection Center, it appears possible to increase survivors in direct proportion to the earliness of detection of the most serious visceral malignancies. This end is accomplished by a well-conceived routine plan of repeated examinations. "Cancer detection" implies the discovery of malignancies prior to the establishment of symptoms or signs which herald their presence.

Methods of Procedure

Prior to admission to the Cancer Detection Center, each patient fills out a questionnaire regarding vital statistics, past history and a system review. Thus, minor symptoms as well as major complaints are made known and can be evaluated. If there is any indication that the patient is truly symptomatic on arrival, examination is refused. The only prerequisites for enrollment in the Cancer Detection Center

*Director, Cancer Detection Center and Instructor in Surgery; †Professor and Chairman, Department of Surgery, University of Minnesota Medical School and Hospitals, Minneapolis, Minnesota.

are: (1) legal residence in Minnesota, (2) lack of symptoms that would require a physician's services, and (3) age limitation—45 years and over for women and 50 years and over for men—which selects that segment of the population in whom the greatest proportion (90 per cent) of all malignancies occurs.

Preparation for examination includes a three day meat-free diet, overnight fasting, and enemas to permit proctosigmoidoscopic inspection. The entire examination requires one day and includes such procedures as gastric analysis,[2] proctosigmoidoscopy, pelvic examination, Papanicolaou smears (female), ear, nose and throat examination with indirect laryngoscopy, general physical examination, complete blood count, urinalysis, testing of stool for occult blood, and a chest roentgenogram (14 by 17 in.). Additional special procedures are performed as indicated. An x-ray of the upper gastrointestinal tract is ordered on the following conditions: (1) achlorhydria or hypochlorhydria (less than 30 degrees free hydrochloric acid), (2) a hemoglobin value below 11 gm. without obvious explanation, (3) the presence of 3 or 4 plus occult blood in the stool, (4) symptoms developing between examinations which in any way might be related to cancer of the stomach, and (5) a family history of gastric cancer in two or more immediate members. A barium enema is ordered if (1) polyps or suspicious lesions are present on proctosigmoidoscopy, (2) there is a hemoglobin of 11 gm. or less without obvious explanation, (3) there is a 3 or 4 plus occult blood in stools, (4) symptoms develop between examinations which might in any way be related to colonic cancer, and (5) there is a strong family history of colonic cancer (i.e., two or more immediate members).

After examination the patient is directed to return to his own physician to whom we send a complete summary of the findings. Biopsies, further evaluation and treatment are carried out under the direction of the private physician or consultant selected by him. If, after six weeks, the patient has not returned to his physician for evaluation of our examination, we send him a letter (a carbon copy of which is sent to the physician), advising that he should consult his personal physician immediately. If he fails to do so, he is dropped from our cancer detection program. Since we stress that annual physical examinations are more important than one single examination, we insist that our patients sign a pledge which requests them, to the best of their ability, to return annually for repeated examinations.

Results

During the 11 year period March 1, 1948 to March 1, 1959, 9,035 patients have been examined at the Cancer Detection Center. Almost an equal number of men and women were seen, 4,317 (47.8 per cent) men and 4,718 (52.2 per cent) women. Some patients underwent only one examination, but since yearly examination is emphasized, some have had as many as 11. The total number of examinations performed was 32,517, of which 16,331 (50.2 per cent) were on men and 16,186 (49.8 per cent) on women. The average number of examinations per patient was 3.60; 3.78 in men and 3.43 in women. Of the 9,035 patients examined, 296 cancers were detected by our Cancer Detection Center. This represents an incidence of 3.28 per cent, or one cancer in every 30.5 patients, or one in every 109.9 examinations; if we exclude skin cancer (of which there were 79 cases), there was one in every 41.6 patients, or one in every 149.8 examinations. One hundred and fifty cancers were detected in men (a cancer incidence of 3.47 per cent) and 146 cancers in women (a cancer incidence of 3.09 per cent). Approximately 40 per cent of cancers were found on first examination and 60 per cent were noted on subsequent examinations.

Fifty-six per cent of patients had absolutely no symptoms in the organ system in which the cancer was diagnosed (or they did not appear severe enough ordinarily to necessitate a physician's evaluation). Cancer of the gastrointestinal tract was detected in 70 patients at the Cancer Detection Center. This included malignancies of the stomach, duodenum, colon and rectum.

The incidence rate of gastrointestinal cancer detected at the Cancer Detection Center was one in every 129 patients (0.77 per cent).

TABLE 1

CANCER OF THE STOMACH

CANCER DETECTION CENTER
(MARCH 1, 1948 TO MARCH 1, 1959)

	SYMPTOMATIC PATIENTS	ASYMPTOMATIC PATIENTS
Total number of cases	10	11
Number dying in less than 5 years	7	6
Number living	3 (30%)	5 (45.5%)
Surviving 5 years	1* (6 yr. 3 mo.)	3 (10 yr. 5 mo.; 8 yr. 6 mo.; 5 yr. 3 mo.)
Surviving less than 5 years	2 (6 mo.)	2 (3 yr. 2 mo.; 10 mo.)
5 Year survival rate	1/8 (12.5%)	3/9 (33.3%)
Combined cases	21	
Over-all survival rate	8/21 (38.1%)	
Over-all 5 year survival rate	4/17 (23.5%)	

*Carcinoid.

The incidence of gastric cancer was one per 430 patients; duodenal, one per 9,035 patients; colonic, one per 411 patients; and rectal, one per 348 patients. Forty-six per cent of gastrointestinal cancers were discovered on first examination. Approximately one-third of patients with gastrointestinal cancer were symptomatic.

Cancer of the Stomach

A total of 21 cases of cancer of the stomach was detected during the period of study, 14 of which involved men and seven women. Eight cases were discovered on the first visit to the Cancer Detection Center and 13 on subsequent annual examinations. Of this latter group, five cases were discovered on the second examination, five on the third, and one case on the fourth, seventh and tenth examination, respectively. Ten patients had symptoms at the time of detection, seven of whom were dead within less than five years after the onset of therapy. Three patients are still living, one of whom has survived six years and three months, and two were operated six months ago. The five year survival rate for this group is 1/8 (12.5 per cent). In the asymptomatic group, 11 cancers were found; six of these patients died within less than five years and five are still living. Of the five patients still living, three have survived five years or more, ranging from five years and three months to 10 years and five months. Two patients are still alive, but were operated on less than five years ago, one surviving 10 months, the other three years and two months. The five year survival rate for this asymptomatic group is 33.3 per cent (3/9 cases). The five year survival rate for asymptomatic patients is less than that noted for patients with symptomatic lymph node-negative cancers of the stomach who have undergone curative resections at the University of Minnesota Hospitals.[3,4] This suggests that our methods for the early detection of gastric cancer are of limited use in early detection and leave much to be desired.

Roentgenographic examination is the best method of detecting gastric cancer,[3] but unfortunately by the time the lesion is demonstrable by this technic, the cancer is often no longer localized to the stomach. This circumstance is evidenced by the fact that only 20.8 per cent of 327 patients with gastric cancer seen at the University Hospitals between 1950 and 1953[4] had the lesion localized to the stomach alone. Thus, almost 80 per cent of patients

TABLE 2

CANCER OF THE COLON

CANCER DETECTION CENTER
(MARCH 1, 1948 TO MARCH 1, 1959)

	SYMPTOMATIC PATIENTS	ASYMPTOMATIC PATIENTS
Total number of cases	6	16
Number dying in less than 5 years	4	3*
Number living	2 (33.3%)	13 (81.3%)
Surviving 5 years	1 (7 yr. 11 mo.)	9 (10 yr. 9 mo.; 10 yr. 6 mo.; 10 yr.; 9 yr. 8 mo.; 8 yr. 8 mo.; 7 yr. 5 mo.; 5 yr. 3 mo.; 5 yr. 1 mo.; 5 yr.)
Surviving less than 5 years	1 (1 yr. 6 mo.)	4 (3 yr. 4 mo.; 1 yr. 3 mo.; 1 yr. 3 mo.; 1 yr.)
5 Year survival rate	1/5 (20%)	9/12 (75%)
Combined cases	22	
Over-all survival rate	15/22 (68.2%)	
Over-all 5 year survival rate	10/17 (58.8%)	

*One patient died of myocardial infarction 3 years and 7 months after surgery.

were found to have positive lymph nodes or distant metastases when seen at this hospital. The reports of the use of exfoliative gastric cytology indicate that it offers much promise as an adjunct in the early detection of gastric cancer. At the Cancer Detection Center we are now employing this technic in all achlorhydric and hypochlorhydric patients in the hope that we may be able to diagnose this lesion before it is demonstrable by roentgenologic means.

One case of asymptomatic cancer of the duodenum was diagnosed. This was a cancer of the first portion of the duodenum. The patient is still living, eight years and two months after surgical excision of the lesion.

Cancer of the Colon

Twenty-two cases of cancer of the colon were detected by the examiners at the Cancer Detection Center. There were seven men and 15 women. Only seven cases were discovered at the initial visit to the Cancer Detection Center. Of the 15 cases diagnosed at subsequent examinations, four were discovered at the second visit, five on the third, two on the fourth, and one each on the fifth, sixth, eighth and tenth annual examination, respectively. Six of these patients were symptomatic and four of them were dead within five years. Two patients are still alive, one having survived seven years and 11 months, the other one year and six months. The five year survival rate for the symptomatic group is 20 per cent. Of the sixteen asymptomatic patients in whom colonic cancer was discovered, 13 are still living. Nine patients have survived five years or more and four patients are still living, but less than five years postoperatively. The maximum possible five year survival rate for the asymptomatic group is 81.3 per cent (13/16), as compared with that for the symptomatic cases, i.e., 33.3 per cent (2/6). The actual five year survival rate of the asymptomatic group is 75.0 per cent (9/12). The combined five year survival rate of all patients in this group is 58.8 per cent (10/17), with a maximum possible five year survival rate of 68.2 per cent (15/22), should all patients who are living at the present time survive five years.

When one compares the results of cancer of the colon with cancer of the stomach, the better prognosis for lesions in the large bowel is

TABLE 3

CANCER OF THE RECTUM

CANCER DETECTION CENTER
(MARCH 1, 1948 TO MARCH 1, 1959)

	SYMPTOMATIC PATIENTS	ASYMPTOMATIC PATIENTS
Total number of cases	7	19
Number dying in less than 5 years	3 (7 mo.†; ½ mo.; 2 yr. 10 mo.)	3 (2 yr. 1 mo.; 4 yr. 7 mo.‡; ¼ mo.†)
Number living	4 (57.1%)	16 (84.2%)
Surviving 5 years	3 (10 yr. 7 mo.*; 8 yr. 9 mo.*; 8 yr. 4 mo.)	7 (8 yr. 11 mo.; 9 yr. 3 mo.; 8 yr. 11 mo.; 8 yr. 7 mo.; 8 yr. 1 mo.; 8 yr. 11 mo.‡; 9 yr. 6 mo.)
Surviving less than 5 years	1 (4 yr. 4 mo.)	9 (4 yr. 3 mo.; 4 yr. 6 mo.; 3 yr. 4 mo.; 3 yr. 2 mo.; 3 yr. 3 mo.; 2 yr.; 1 yr. 10 mo.§; 2 yr. 1 mo.; 3 yr. 3 mo.)
5 Year survival rate	3/6 (50%)	7/10 (70%)
Combined cases	26	
Over-all survival rate	20/26 (76.9%)	
Over-all 5 year survival rate	10/16 (62.5%)	

*Dead.
†Died of postoperative complications.
‡Died of bowel obstruction—no cancer.
§Carcinoid.

evident. The best possible five year survival rate for those patients with carcinoma of the stomach, should they all survive five years, would be 38.1 per cent (8/21). The actual five year survival rate at present for that group of patients with cancer of the stomach is 23.5 per cent (4/17). This is somewhat better than the five year survival rate of patients seen at the University Hospitals during the period 1950 to 1953, which was 14.7 per cent, but it is quite evident that there is much room for improvement.

Cancer of the Rectum

During the period from March 1, 1948 to March 1, 1959, 26 cases of cancer of the rectum (18 men and 8 women) were diagnosed at the Cancer Detection Center. The majority (16) of cases of cancer of the rectum were discovered at the first visit to the Cancer Detection Center. Of the 10 cases discovered on subsequent visits, only three were found on the second examination, two on the third and sixth visit, respectively, and one each on the fourth and seventh visit to the Cancer Detection Center. Of this group seven were symptomatic and 19 were asymptomatic. Of the seven patients who had symptoms when seen at the Cancer Detection Center, three died within five years and four are still alive. Three of the remaining four patients have survived periods ranging from eight years and four months to 10 years and seven months. One patient is alive four years and four months after surgery.

Of the 19 patients without symptoms in whom the cancer was diagnosed, 16 are still living for a possible maximum five year survival rate of 84.2 per cent. Of these 16, seven have survived five years; the periods range from eight years and one month to nine years and six months. Nine patients are still living, though less than five years; the periods range

from one year and 10 months to four years and six months. The actual five year survival rate for the symptomatic group is 50.0 per cent (3/6), as compared with the asymptomatic group's rate of 70.0 per cent (7/10). The maximum possible five year survival rate for all patients with rectal cancer is 76.9 per cent (20/26). The actual five year survival rate at present is 62.5 per cent (10/16). This is still considerably better than the survival rate for that group of patients who presented themselves to the University Hospitals with symptoms of rectal cancer.

In addition to the malignant neoplasms encountered, certain precancerous conditions were detected. These included 3,083 rectal and colonic polyps and 45 gastric polyps. If one considers these lesions as being premalignant, the protection afforded by their early detection and excision is as important in the treatment of cancer as the detection of the early lesion. It is of some interest to note that only two cancers of the gastrointestinal tract were missed by the examiners at the Cancer Detection Center. They were two carcinomas of the colon. No cases of cancer of the stomach or rectum failed to be diagnosed.

Over-all Results of Therapy

Of the 70 cancers of the stomach, duodenum, colon and rectum diagnosed at the Cancer Detection Center, 44 patients (62.9 per cent) are still living or have survived five years or more. The present five year survival rate for all cases is 49.2 per cent (25/51); for the symptomatic group, 26.3 per cent (5/19), as compared with the asymptomatic group, 62.5 per cent (20/32). (If we assume that all patients who are alive today will survive at least five years, the maximum possible five year survival rate for all patients is 62.9 per cent [44/70]; for the symptomatic group, 39.1 per cent [9/23], as compared with 74.5 per cent [35/47] for the asymptomatic group.) Thus, the actual and possible five year survival rates of the asymptomatic group are at least twice that of the symptomatic group. In addition, if one compares these results with reported five year survival rates of 25 per cent to 33 per cent, it is obvious that detection and treatment of asymptomatic cancer offer a much greater chance of cure.

A most interesting finding was that of the 29 cancers of the breast discovered at the Cancer Detection Center, 26 were in patients who are still living and well. Only one patient of the 19 with asymptomatic breast cancer has died. Of the remaining 18 patients in the asymptomatic group who are still living, nine have survived five years or more. Thus, the actual five year survival rate for asymptomatic breast cancer detected at this Center is 90.0 per cent (9/10). The maximum possible five year survival in this same group of patients is 94.7 per cent (18/19).

Summary

During the first 11 year period, 70 cases of gastrointestinal cancer were detected at the Cancer Detection Center of the University of Minnesota Hospitals. The five year survival rate of these patients was two to three times better than that reported for cancer throughout the country. The diagnosis and treatment of asymptomatic alimentary tract cancer offer a cure rate twice that of symptomatic cancer.

The parallelism of aging and cancer incidence will tend to produce a population group highly susceptible to this disease. The results of the Cancer Detection Center convincingly show that presymptomatic gastrointestinal malignancy can routinely be disclosed by thorough periodic physical and laboratory examinations and that malignancies discovered at this early stage will offer the patient an increased opportunity for cure.

REFERENCES

1. Hitchcock, C. R. and Sullivan, W. A.: Increasing the survivors of cancer through asymptomatic diagnosis of malignant disease. Surgery 39:54-69 (January) 1956.
2. Hitchcock, C. R., Sullivan, W. A. and Wangensteen, O. H.: The value of achlorhydria as a screening test for gastric cancer; a 10 year report. Gastroenterology 29:621-628 (October) 1955.
3. Shahon, D. B., Horowitz, S. and Kelly, W. D.: Cancer of the stomach: An analysis of 1,152 cases. Surgery 39:204-221 (February) 1956.
4. Shahon, D. B., Lunseth, J. B. and Wangensteen, O. H.: Gastric cancer follow-up studies at the University of Minnesota Hospitals, 1950-1953. Univ. Minnesota M. Bull. 30:366-386 (April 15) 1959.

Value of Periodic Examinations in Detecting Early Lung Cancer

ROBERT B. BROWN*

National Naval Medical Center, Bethesda

ROBERT B. BROWN

It would appear that the Naval Medical Department is in a uniquely favorable position to answer, at least in part, the question implied in the title of this presentation. All active-duty personnel of the Navy and Marine Corps are required to have annual x-ray examinations of the chest. In addition, for all officers and many of the enlisted men these are combined with physical examinations. Admittedly, this population does not constitute a random sample in respect to age, the upper limit being 62 years. However, it does include the sixth decade, that period in which bronchogenic carcinoma approaches its peak incidence.

Eighty-one malignancies of the lung were diagnosed in the eight year period between 1950 and 1957, inclusively. The records on these cases were procured and a current follow-up was obtained on all of those patients still living. Pertinent data were recorded with particular attention directed to determining for every case whether the finding that led to further study and ultimate diagnosis was the result of a routine x-ray or physical examination. The cases so discovered will be referred to as the detected group. The remainder will be designated the undetected group, which includes not only those patients who sought medical advice because of symptoms referable to the tumor but also a few in whom the diagnosis was made incidental to studies for an unrelated condition.

*Captain, M.C., United States Navy; Chief of Surgery, National Naval Medical Center, Bethesda, Maryland.

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

Findings

Twenty-six of the 81 cases of lung malignancy were discovered at routine examinations (table 1). Taken at face value it would appear very gratifying that approximately one-third of these tumors had been so detected. Before too strenuous rejoicing, however, this finding must be subjected to further analysis along at least three pertinent lines:

TABLE 1

MODE OF DETECTION

	Number	*Per cent*
Total cases, cancer of the lung	81	
Discovered at routine examination	26	32
Discovered as a result of symptoms	49	68
Discovered incidentally while studying other diseases (sinusitis; nose cancer; knee operations, etc.)	6	

1. How many annual examinations were performed in bringing to light these 26 lesions?

2. Were the tumors discovered by routine examinations actually earlier lesions than the others in terms of (a) lack of symptoms? (b) operability and resectability? (c) metastases?

3. What are the survival data for the two groups?

1. *Yield of annual examinations in terms of carcinoma of the lung:*

It is estimated that about seven million annual routine examinations were performed on Navy and Marine Corps personnel between 1950 and 1957, inclusively. These examinations yielded 26 malignant lesions of the lung, approximately one case for every 270,000 examinations. This yield is necessarily low because of the age structure of the Navy. For purposes of discussion, it is more realistic to consider the yield among those aged 50 and over. For this group it is estimated that one case of lung cancer was discovered for every 4000 routine examinations performed.

2. *Evidence that the lesions discovered at routine examinations were earlier lesions than the others:*

a. *Lack of symptoms*—The fact that an abnormal finding on routine examination was the reason for instigating further study which led to the diagnosis does not imply that the patients in this category were all asymptomatic at the time of examination. To the contrary, it was found on review of the clinical charts that in only 13, or one-half, of the 26 cases involving lesions noted on routine examinations were the patients symptom-free. The other 13 patients had significant symptoms that could reasonably be attributed to the tumors. These symptoms varied from minimal ones, such as recent nonproductive cough or change in character of a chronic cough, to symptoms and signs of a moderately advanced obstruction of the superior vena cava. In only three cases of the undetected group were the patients free of symptoms referable to the tumor, and these were all cases discovered as a result of studies made for other medical conditions.

b. *Operability and resectability*—The data with respect to operability and resectability are summarized in table 2. Eighty-eight per

TABLE 2

OPERABILITY AND RESECTABILITY

GROUP	TOTAL	NOT OPERABLE	OPERABLE		
			Total	*Resectable*	*Not Resectable*
	Number of Cases				
Total	81	19	62	45	17
Detected	26	3	23	18	5
Undetected	55	16	39	27	12
	Per cent				
Total	100.0	23.4	76.6	55.6	21.0
Detected	100.0	11.5	88.5	69.2	19.3
Undetected	100.0	29.1	70.9	49.1	21.8

TABLE 3

METASTASES

GROUP	TOTAL	CONFINED TO LUNG	METASTASES		
			Total	*Distant Metastases*	*Local Extension**
	Number of Cases				
Total	81	17	64	15	49
Detected	26	6	20	1	19
Undetected	55	11	44	14	30
	Per cent				
Total	100.0	21.0	79.0	18.5	60.5
Detected	100.0	23.1	76.9	3.8	73.1
Undetected	100.0	20.0	80.0	25.4	54.6

*Including regional lymph node metastases.

cent of those cases discovered at routine examination were operable as compared to 71 per cent of the undetected group. Sixty-nine per cent of the tumors in the detected group were resectable, as against 49 per cent in the undetected group. Of the 18 patients in the detected group who did have resections, nine underwent pneumonectomies, eight had lobectomies, and one had a segmental resection. In the undetected group, 27 had resections of which 11 were pneumonectomies, 14 were lobectomies, and two were segmental resections.

c. *Metastases* (table 3)—Distant metastases were demonstrated on initial workup in only one, or 4 per cent, of the patients with tumors picked up on routine examination, while they were present in 25 per cent of those whose lesions were not so discovered. These metastases constituted the most frequent contraindication to surgery. Bronchoscopic demonstration of carinal involvement accounted for the two other patients not operated on in the detected group; a positive Papanicolaou test of pleural fluid and patient refusal constituted the additional reasons for "inoperability" in the undetected group. Local extension, including that to regional nodes, was more frequent in the detected group, but was of a nature to contraindicate resection less frequently than in the undetected group.

In 23 per cent of the cases discovered at routine examination there was no demonstrable extension of the lesion beyond the confines of the lung, either at operation or on microscopic examination of the resected tissue. This was true of 20 per cent of the cases in the undetected group. However, it must be pointed out that this latter group was weighted favorably in two respects. Two of the cases were those discovered on study incidental to hospitalization for another reason (not for symptoms referable to the tumors) and from the standpoint of pathology these cases include the two carcinomas *in situ* and one malignant adenoma.

In respect to all three criteria, lack of symptoms, resectability, and presence and extent of demonstrable metastases, the cases discovered on routine examinations may, as a group, be considered earlier cases than the others.

3. *Survival data:*

The modified life table method was used to obtain survival data and the results are shown in table 4. At each interval from three months to five years, the figures are slightly, but not significantly, higher for the detected group. The five year survival rate for this group was 22 per cent, as compared to 18 per cent for the undetected group. Actual five year survival rates computed for the cases diagnosed

TABLE 4

PATIENTS WITH CANCER OF LUNG SURVIVING THREE MONTHS TO FIVE YEARS AFTER DIAGNOSIS*[1]

GROUP	PER CENT SURVIVING						
	Three Months	*Six Months*	*One Year*	*Two Years*	*Three Years*	*Four Years*	*Five Years*
Detected	92	69	50	38	28	22	22
Undetected	85	65	47	32	26	18	18

*Based on modified life table analysis.

TABLE 5

DISTRIBUTION OF HISTOLOGIC TYPES

HISTOLOGIC TYPE	TOTAL	DETECTED GROUP	UNDETECTED GROUP
All types	81	26	55
Squamous or epidermoid	18	8	10
Adenocarcinoma	10	3	7
Anaplastic	25	6	19
Small round cell	8	4	4
Alveolar or bronchiolar	7	3	4
Carcinoma *in situ*	2	–	2
Malignant adenoma	2	–	2
Sarcoma	1	–	1
Not recorded	8	2	6

between 1950 and 1954 are quite comparable, 21 per cent and 16 per cent for the detected and undetected groups, respectively.

As pointed out in respect to distant metastases, the undetected group is weighted favorably for survival from the standpoint of the pathology in that it includes both cases diagnosed as carcinoma *in situ* and the only two malignant adenomas in the study. Otherwise, the distribution of the various histologic types of lung cancer within the two groups is not so different that it should have influenced survival significantly (table 5). The effect on survival of postoperative irradiation or nitrogen mustard therapy which was used sporadically throughout both groups is impossible to assess.

Discussion

Be it understood, annual examinations are not carried out for the sole purpose of detecting cancer of the lung. If this were so, it would be hard to justify them on the basis of a yield of one case detected for every 270,000 examinations. However, the much more realistic figure for those aged 50 and over would be reasonable to support in economic terms if lung cancer detection were the only objective.

Satisfaction at picking up one-third of this group of lung cancers at annual examinations is tempered by the discouraging fact that two-thirds were not so discovered. Two leading possibilities for increasing the percentage of lesions detected by routine examinations suggest themselves: (1) Decrease the interval between examinations; (2) increase the scope of the examinations.

It is hardly practicable, particularly in the military, to cut the interval between routine examinations to less than one year. Moreover, our data would indicate that examinations at intervals as short as six months will not solve the problem. Many of our patients had had routine examinations, with negative radiograms of the chest, only one or two months prior to admission for symptoms. Nevertheless, those in the older age group in the Navy and Marine Corps are being encouraged to report

for *voluntary* medical checkups in the interval between the compulsory annual examinations. A study at some future date of the response to this invitation and the yield in terms of increased detection of lung cancer by the interval examinations may be revealing.

It has been indicated that not all of the population involved in this study had a complete physical examination in addition to the annual x-ray examination of the chest. Had the combination been applied to all it is possible that the detection of lung cancers might have been significantly increased. This is questionable. In all but one of our cases that were discovered at routine examination there was an abnormality demonstrable by chest roentgenograms in addition to whatever other signs and symptoms may have pointed to the diagnosis. In the one exception, the patient was hospitalized because of albumin found on routine urinalysis and the diagnosis of lung cancer was made as a result of the ensuing studies.

The breakdown of the detected group into those with and those without symptoms is deserving of further comment. That half of these patients already had symptoms and had not previously sought medical advice emphasizes the importance of continuing education in respect to early symptoms and their significance. Not one of this subgroup with symptoms has survived three years.

On the other hand, the data on the 13 patients with the asymptomatic lesions clearly demonstrate that increased detection of tumors in this stage is the real contribution of periodic examinations in respect to lung cancer. All were operable, all but one resectable, and three of the nine patients diagnosed in the period 1950 to 1954 have survived five years or longer. These data are even more significant when it is noted that none of the malignant adenomas or carcinomas *in situ* are included in this group.

Summary

1. This study is based on 81 cases of lung cancer discovered in Navy and Marine Corps personnel between 1950 and 1957, inclusively.

2. One-third of these tumors were detected by routine annual examinations.

3. The group of cancers so detected were slightly more favorable lesions in respect to operability, resectability, metastases and survival, as compared with those that were not so discovered.

4. Possible means for increasing the yield from periodic examinations in terms of lung cancer are discussed.

5. Not all of the lung cancers discovered at annual examinations were asymptomatic lesions; only half in this study. This finding reaffirms the importance of continuing education in respect to early symptoms of lung cancer and the urgent need for examination in respect to them.

6. Finally, data are presented on the 13 tumors which were discovered in the asymptomatic stage to point up the relatively favorable findings and prognosis for lesions in this category. The most significant contribution of the annual examinations in respect to cancer of the lung was the detection of this group of tumors before symptoms developed.

The author wishes to express appreciation to the Statistical Division and the Medical Qualifications Division of the Bureau of Medicine and Surgery for their invaluable assistance in the preparation of this article.

REFERENCE

1. Berkson, J. and Gage, R. P.: Calculation of survival rates for cancer. Proc. Staff Meet. Mayo Clin. 25:270-286 (May) 1950.

The Problem of the Precancerous Lesion

FRED W. STEWART*

Memorial Center for Cancer and Allied Diseases, New York

FRED W. STEWART

It is difficult to discuss precancerous lesions from a pathologist's viewpoint before a group not made up largely of pathologists. I have elected to note certain principles and to illustrate them with a few examples. The first principle I can encompass in a few sentences. It is that by finding to your satisfaction that something is precancerous you haven't explained very much. You still do not know what caused the cancer. There is no direct uninterrupted line from normal to precancer to cancer. You still have to add something. A lesion is to be thought of as precancerous if cancer is added more often to it than when it is not there.

The second principle is that because a lesion looks quite like a malignant tumor, perhaps to such an extent that a pathologist not familiar with the process or who works without adequate clinical information will mistake it for cancer, it need not be either cancerous or precancerous. In the beginning, to illustrate, one may select lesions of the skin.

Epithelial Lesions

Prominent among lesions of the skin is what is variously called molluscum sebaceum, verrugoma, idiopathic pseudoepitheliomatous hyperplasia, keratoacanthoma, self-healing prickle-cell epithelioma, the number of names testifying to the confusion in the subject. Now I have read that there are means of distinguishing this lesion from squamous cancer microscopically, but I myself confess to quite a bit of difficulty from time to time. I think there are three things that aid the pathologist. One is the time element, and it will be found that the lesion is apt to be of relatively short duration. Another is lack of predisposing features in the skin, a lack that of course *may* not exist. A third is the tendency one sees histologically for the lesion to sort of die out by overmaturation in its deeper layers. Despite this, if one focuses on areas of keratoacanthoma he will see things that under proper setting would call for a diagnosis of cancer; yet, so far as we know, the fact that this lesion looks like cancer does not even make it actually *pre*cancerous.

Let us cite some other examples: Some

*Pathologist (Emeritus), Memorial Center for Cancer and Allied Diseases, New York, New York.

seborrheic papillomas look quite alarming and yet have nothing especially to do with the lesion they resemble, namely, basal cell carcinoma. Occasionally, not often, we see lesions attached to the skin, usually diagnosed clinically as sebaceous cysts. On removal, the surgeon will find a solid tumor, or perhaps a mixture of solid grayish-yellow areas and softened areas, and not infrequently he will find bony hard portions. This is the so-called benign calcifying epithelioma of Malherbe. The lesion can be confused with cancer by the unwary, and indeed I recall such confusion not by a tyro but by a professor of surgical pathology in a prominent medical school a few years ago. Again, this is not precancerous despite its resemblance to squamous carcinoma.

In mucous membranes confusing lesions occur, and most often confused with squamous carcinoma is granular myoblastoma. Its most common site is the tongue, although it may occur elsewhere, for example, in the larynx where, since it is unexpected, the chance of confusion with cancer is even greater. Luckily away from the tongue the lesion is rare. This lesion looks like squamous cancer and is not even precancerous. Two mucosal inflammatory lesions may be confused with cancer: One of these is tubercle where confusion is not easy, although I have seen both buccal and laryngeal tubercle diagnosed as cancer. The second is blastomycosis where resemblance to carcinoma may be striking. Of course, cutaneous lupus may be precancerous, especially after treatment by x-ray, whereupon how much is lupus and how much is radiation is not easily determined when the matter of precancerousness versus radiation etiology is assessed. A startling amount of glandular proliferation may simulate cancer in instances of tubal or endometrial tuberculosis, and again that simulation is unrelated to adenocarcinoma.

Certain specific situations yield histologic patterns that are very close to the cancerous, yet, so far as we know, they bear no relation to neoplasia. I might cite the metaplasia in lung and intestinal mucosa seen after chemotherapy in leukemic children. Startling changes may appear in a specific type of accidentally occurring pneumonitis in the course of chemotherapy by antileukemic agents, and the process mimics cancer.

Lesions of Connective Tissue

So far, discussion has illustrated epithelial lesions that may simulate cancer but are not precancerous. There are a few lesions of connective tissue in the same category. Prominent among them is the lesion of joints and tendons called pigmented villonodular synovitis, which may closely simulate a malignant tumor in those areas. We have saved a number of extremities from planned amputation because of a pathologist's error in this direction. Again, this lesion is neither cancer nor precancer. Another lesion related to subcutaneous tissues and mostly superficial fasciae is the process called infiltrative fasciitis. In my experience, infiltrative fasciitis has repeatedly been called fibrosarcoma, and amputation has been advised for this innocent though occasionally alarming-looking lesion. When fasciitis involves connective tissues between individual striated muscle fibers, I have seen it confused with rhabdomyosarcoma. The keys to thinking of infiltrative fascitis instead of sarcoma are superficiality of location (not *always* the case), shortness of duration, slight pain or tenderness, and perhaps a little edema. Infiltrative fasciitis, in spite of its appearance, is not presarcomatous.

Cytologic Criteria

A diagnosis of cancer has, of course, attained something of a cytologic level during the past couple of decades. Cytologic criteria exist for such diagnosis. Cytologists rely on such things as nucleocytoplasmic ratios, appearance of nucleoli, hyperchromatism, but none of these are meaningful out of context, so to speak. If I wished to demonstrate one of the most cancerous-looking cells the human body can create, I would pick the so-called Askanazy cell in involuting thyroid glands. Such cells can even occur in aggregates, hence simulate even more a carcinoma of the thyroid. So far as we know, this cytologic lesion that looks like cancer is not precancerous. Other examples of cytologic patterns not precancerous but resembling cancer are the Arias Stella cells in endometrium and endocervix,

the occasional big nuclei one sees in cells of caruncles, and the large nuclei often seen in seminal vesicles.

Before one talks about something being precancerous, he has to know not only histology but disease. Precancerousness is more than a mere microscopic pattern. I think the crowning example of resemblance to cancer and the absence of even precancerousness is seen in the early placenta. Here not only are the resemblances between early normal placenta and choriocarcinoma so striking histologically that it requires virtually second sight to tell the difference, but the behavior for a limited span of the life of the placenta is that of a real cancer. It destroys, it invades, it derives blood supply from "abnormal" means—blood lakes—and it can invade vessels and disseminate to viscera without constituting cancer. Its very growth rate exceeds that of most highly malignant tumors.

One cannot but contrast the seemingly bad pattern of many of the lesions listed that do not become cancer with the more innocent pattern of those that do; i.e., oral leukoplakia, or those that we think really are, such as laryngeal pachydermia or the extremely low-grade everted papillary cancers that spread over areas of the oral cavity and long defy microscopic diagnosis of cancer, unless you happen to be familiar with the type.

Frequency and Duration

A third factor in precancerousness involves the matter of frequencies. How often does cancer have to occur in a definite setting in order to have that setting, that lesion, certified as a precancerous state? For that matter, how long does it have to be present? To illustrate: All pathologists recognize that lesion of the breast variously called sclerosing adenosis, fibrosing adenomatosis, and myoepithelial tumor of Hamperl. It is highly proliferative in appearance, although mitotic activity is minimal to absent. Its spontaneous course is in the direction of involution and fibrosis. Rarely is it seen in florid form after the menopause, when breast cancers are more common. On very rare occasions cancer is seen arising in sclerosing adenosis. Does this make sclerosing adenosis a precancerous lesion? By our definition, it does not. As part of my reasoning for that point of view, I can state that by no means in this unusual event is the cancer necessarily confined to the areas of adenosis, but it is seen also to originate in parts of the breast not previously the site of the adenosis. The cancer has arisen in the breast and not in some special process within the breast exclusively; hence it is wrong to call that special process precancerous. It would have come irrespective of the adenosis, a chance acquaintance, not a near relative.

Again stressing the matter of frequencies. contrary to what has been said about the lack of cancer in large breast papillomas, I have on very rare occasion seen such cancer, but with such rarity I would not think of regarding the intracystic papilloma in the precancerous category. Even less could it be so regarded than might fibroadenoma, because the latter does rarely become cystosarcoma phyllodes and *may* be malignant.

The question of breast cancer and cystic mastopathy has for the most part been dealt with rather superficially. Much published data fail to indicate specific constituents of the process and figures have been reported indicating some 11 times higher frequency of cancer in premenopausal women all the way down to the no-difference level, depending on just what people were calling chronic cystic mastitis. One is never sure how much material per case was used to establish criteria and how much was known about the presence of such minutiae as *in situ* lobular carcinoma in initially excised specimens. Evidence makes some association likely but, surely, we could stand more proof.

We have, to be sure, seen cancer arising in ducts at the site of papillary to solid proliferation, but in the same breast one will see the cancer developing outside of such areas, in ducts and lobules, so once more the interrelation in the sense of precancerousness of the proliferation is obscure. It is sad, indeed, but once we have taken something out and studied it, we cannot put it back and observe it for the next decade to see what it will do. If these ductal proliferations are precancerous, the

time for the cancer development is *probably* long. Indeed, I have suggestions that mammary cancer in pathologically recognizable form may exist within mammary ducts for a decade without infiltrating. Hence one might assume, again without proof, that the precancerous phase, if such we call it, may be even longer. Certainly there is much proof that it is spontaneously interrupted by atrophy and fibrosis.

We sorely need large numbers of long follow-up studies on cases where we have dubbed the intraductal proliferation as cytologically atypical in locally excised specimens. A number of such cases followed do not yield evidence for the precancerousness of such lesions so far. Contrast this with the insignificant-looking tiny foci we have called lobular carcinoma *in situ*. The least of these is a danger signal. When this process is handled by local excision only, the patient may get by, but she has a 25 per cent chance of having infiltrating mammary carcinoma in five years and a 37 per cent chance of having it within seven years. What 10 years will bring, I can only surmise. I cite this because I want to show how easy proof is when you *really* have something. One must show something in frequency over and above the very rare, in order to say that a lesion shall be called precancerous. In the breast, whereas cytologic change of a cancerous nature may occur in ducts that are hyperplastic, multi-layered and papillary, it can also occur in ducts that show no such change, hence appearing quite *de novo*.

Lesions of Gastrointestinal Tract

A few words concerning the gastrointestinal tract are essential, especially because of some controversy of late. In recent years I have had occasion to study many plaques of mucosal hyperplasia and many polyps found during proctoscopic and sigmoidoscopic examinations of normal patients in the detection clinic. I have seen every transition from hypertrophied mucosal plaques into polyp, into villous tumor, into carcinoma *in situ*, single or multiple within a single small polyp or villous tumor, and into infiltrating cancer. This does not mean that a diagnosis of polyp or villous tumor or of *in situ* cancer within a polyp calls for treatment as if the patient had cancer any more than it does in the case of *in situ* carcinoma of the cervix. It calls for repeated observation over the years, especially since other studies[1] have shown that individuals who have a polyp tend to get more polyps; that those who start with multiple polyps have a bigger chance of getting more than do those with single ones; that the chance of cancerous polyps was nearly twice as great where the polyps were multiple as when they were single; that twice as many deaths from cancer occurred in the cases of multiple polyps as in those of a single polyp. In 57 per cent of cases of cancer *in situ* involving polyps there were no subsequent polyps in five years after local biopsy and simple surgery. But of 56 cases of this type of cancer, more polyps developed in about 43 per cent, and real cancer developed in eight.

Cancer in cases of polyps is overdiagnosed, just as is *in situ* cancer of the cervix, this being part of the total enthusiasm for early cancer diagnosis. Where *in situ* carcinoma occurs in a villous adenoma, it is a danger signal. According to our data, invasive cancer develops in nearly 40 per cent of villous tumors. Dr. Foote has told me that in over 20 years he has seen but one stalked polyp with cancer and without stalk invasion that metastasized and that was cecal and small (some 1.5 cm. with a 0.75 cm. stalk) and it filled the liver. In a second probable case the primary site was rectal, but the memory of facts is obscured. With this frequency the chance of metastasis from a stalked polyp with cancerous change is about that of being struck by lightning. You *can* be struck.

For a long time I doubted the precancerous nature of ulcerative colitis, since we saw little evidence of it in our own material. This doubt has vanished with increasing evidence of the frequency of the association. Recent data from Sweden[2] show that carcinoma of the large bowel will develop in as many as 33 per cent of cases of ulcerative colitis of 10 to 20 years' duration. The histologic steps in the transformation are not clear, since most of the cancers are advanced when their presence is first realized. The precancerousness of ulcerative

colitis appears presently to contrast with any similar finding in other ulcerative states of the large bowel, thus emphasizing some specificity of factor. It must, however, be said that areas where chronic recurring amebiasis occurs often are apt to be poorly serviced medically and the people there have shorter life spans. The ulcerative state is also less chronic. Intestinal tuberculosis either is cured or terminates lethally before it has existed for a time comparable with most ulcerative colitis.

To one who sees the extreme lymphoid hyperplasia and infiltration of regional enteritis it is curious that it has no apparent relation to intestinal lymphosarcomatosis. In some cases distinction between these entities is most difficult. The whole small bowel is virtually free from cancer and from lesions one thinks of as precancerous, viz., polyposis. Somewhere in the exemption from cancer of this large mucosal area, with much cancer above and below it, there should be an answer to a big secret.

I am not entering in the old controversy about the precancerousness of peptic ulcer. I can only say that I have seen almost no instances where proof could be absolutely defended for such status. Gastric polyp is a very rare precancerous lesion, mostly in addisonian anemia. Gastric atrophy also appears precancerous in this disease but not necessarily in its absence.

Versé plaques that are really *in situ* gastric carcinomas can exist for many years prior to becoming clinical cancer, hence can merit the classification "precancerous" in the clinical sense though not in the pathologic. Whether *in situ* carcinoma should be called cancer or precancer is a little academic, for just as you must have something added to precancer to make it a cancer, so too must something happen to *in situ* cancer to make it clinical invasive cancer. It just happens with greater regularity.

Laennec's cirrhosis and pigmentary cirrhosis are common predecessors to human liver cancer. These lesions fulfill all requirements one defines for the precancerous. In areas of endemic liver cancer, however, cancer may be several times more common than cirrhosis. Nothing is known of precancerous lesions of extrahepatic bile ducts and gallbladder, for the earliest changes one sees are true *in situ* carcinomas. In the recent experimentally produced cancers of the gallbladder and bile duct in dogs, reported by Sternberg and associates[3] as caused by a miticidal agent, inflammation is conspicuously absent and one sees *in situ* cancer initially, of course, with cytologic abnormalities that some will call precancerous. Mucosal hyperplasia and adenomas were thought to be precancerous.

Lesions of the Lung

There has of late been much interest in precancerous lesions of the lung due to increasing importance of cancer in that area. That *in situ* carcinoma antedates infiltrating cancer is certain, if for no other reason than that there is no other way for cancer to begin. As with the uterine cervix, agreement does not exist on where metaplasias and atypias end and *in situ* carcinoma begins. There probably is no ascertainable sharp division. The same lesions may be found in the trachea where, in view of the fact that tracheal cancer is exceedingly rare, their significance, if such they possess, must be less. The fact that similarly appearing lesions may vary in significance in different sites is not at all unreasonable, nor does it detract from evidence merely because we do not know why such is the case.

The so-called terminal bronchiolar carcinomas seem on occasion to develop in old cicatrices, sites of ancient tuberculosis, or in old pulmonary infarcts. Thus they are an example of scar cancers, like those of burn scars, or cancers that occur in old hyalinized, previously benign mixed tumors of salivary glands, or the cystosarcoma phyllodes that springs up in an old hyalinized fibroadenoma, and like the rare squamous cancer that develops in what was, we assume, misplaced stratified epithelium included many years before in the course of ancient trauma. These cicatricial cancers are far too rare to think of scars as precancerous lesions.

Cervical Lesions

The popularity of cytologic screening has resulted in much study of the cervix uteri. We

have for some years now been participants in a follow-up study of lesions variously diagnosed as *in situ* carcinoma, mild to severe atypias, warty dyskeratosis and leukoplakia, and the full import of these diagnoses to me is still very obscure. It appears that *in situ* carcinoma is surely a precursor for infiltrative cancer. It may take many years to become clinical cancer—up to 13, in our experience. On the other hand, it also appears that on occasion this lesion is interrupted by means that appear far short of what might be considered any treatment for cancer. To me the explanation that a small biopsy has removed disease is unsatisfactory. After long interruption it may recur.

It appears that the various atypias, dyskeratoses and leukoplakias can merge with *in situ* carcinoma. Indeed others will have to tell me just where the line is to be drawn. I do not pretend to know how often, how rapidly, with what regularity, and with what chance of interruption, remission or disappearance these lesions progress; hence, I would only assert that these cervical abnormalities should be subjected to recurrent investigation and that one should try not to lose a patient where these features have appeared. Also, one should not rush into some radical program. Our own position on these lesions is that of still trying to gather sufficient follow-up data to enable us to make up our minds, and it is going to take quite a long time. The whole subject seems more complicated than it did some years ago. *In situ* cervical cancer was recognized years ago, and we still do not know it adequately, nor are we sure yet of our evaluation of its precursors.

In the endometrium polyps and cystic and adenomatous hyperplasia are precursors of endometrial cancer. In the ovary I know of no benign tumor that may not be a precursor to a malignant one. For vulvar cancer, there is senile vulvitis; in younger patients the precursors are lymphogranuloma venereum, vulvar psoriasis, and possibly lichen sclerosus.

Lesions of the Bladder

The bladder is an interesting site for precancerous lesions. One, of course, is the papilloma, not the floating, villous frond type, but the wartier, broader-based variety, especially when it is multiple. Bladder leukoplakia is another, and one must distinguish leukoplakia from epidermoidization. Long-standing bilharziasis produces regenerative squamous papillary lesions that are inflamed, incrusted, and sources for bladder cancer, usually squamous. Patches of intestinal metaplasia have given rise to glandular cancers, although these must be a rare source for such cancers since the number of the latter is very low when compared to the usual urothelial cancers. Extrophic cancers of the bladder are apt to be of this type. The various chemically induced industrial cancers of the bladder that I have seen have not exhibited precursor lesions of any classic pattern.

Unfortunately, we see results of biopsies only in early cases and lack total bladder material. Inflammation is common, but inflammation is common in any bladder cancer and is probably secondary to the cancer. One must remember that the cancerous mucosa is a poor barrier and recall that the principal function of a stratified mucosa, like the skin, is to keep the inside in and the outside out, a remark I once heard from the late Charles R. Stockard. The cancerous mucosa does not do the job. The earliest lesions in this group I have seen already were all cancers, although *in situ* in position, or perhaps only spotty, individual, hyperchromatic, large nucleated cells were seen here and there, like Paget cells in a nipple. It is, however, known that papillomas can occur simultaneously with cancers or antedate the cancer in the industrial tumor field. I believe that an understanding of the responsible agent is probably more important than the histology of the papilloma in judging the precancerousness of the latter. Nasty-looking *in situ* lesions are common and multiple in the chemically injured bladder.

Lesions of the Skin

The skin is the site of many lesions, and whenever a cancer appears the lesion seems to be readily accepted as precancerous. Specific precancerous lesions are not numerous. There are sunlight keratoses, chemical kera-

tosis, radiation dermatitis, xeroderma pigmentosum, arsenical keratoses, lymphopathia venereum (for anal cancer), kraurosis vulvae, psoriasis and lupus, especially when irradiated. Note that these are specific lesions etiologically. I do not mention Bowen's disease for cytologically that is really *in situ* carcinoma. All of these lesions are accompanied by chronic inflammation but the inflammation is not primary. The precancerousness depends on specific etiology and has nothing to do with inflammation as such.

Musculoskeletal Lesions

Precancerous lesions of the musculoskeletal system tend to be highly specific and their recognition as such rather than their histologic patterning is the key to knowledge that the precancerous state exists. Thus, osteitis fibrosa cystica is not presarcomatous, while the solitary lesion that simulates it microscopically, namely, the giant cell tumor of bone, surely is and especially if irradiated. Paget's disease is a common source for both single and multiple osteogenic sarcoma; nonosteogenic fibroma is not a source; fibrous dysplasia very rarely is; central chondroma frequently is a source in middle or later life; Ollier's disease rarely is, and the solitary exostosis cartilaginea virtually never. Capillary angiosarcoma may develop from bone angioma on rare occasion. No predecessor lesion is known for such lesions as Ewing's tumor or for reticulum cell sarcoma of bone.

In soft tissues the bulky lipoma can be the seat of liposarcoma, the plexiform neuroma the source for neurosarcoma (malignant neurilemoma), although the solitary encapsulated palisading neurinoma, which may look quite bad, seemingly is not. No one has ever seen the beginnings of a rhabdomyosarcoma. Of course, malignant transformations of leiomyomas of viscera are well known. The commonest source for vigorous proliferation of muscle nuclei is trichinosis which, so far as I know, has never been incriminated as presarcomatous. As in the case of epithelial tumors, indications are toward specificity and not generality, and the more one learns of the cause of a lesion, the more specific this lesion becomes. Witness, for instance, the high frequency of osteogenic sarcoma after the ingestion of radioactive material; the absence of osteogenic sarcoma in long-standing osteomyelitis, caisson disease and tuberculosis, all equally disturbing to bone integrity; and the total noncancerogenic effect of the most severe injury to bone, namely, fracture. In radiation lesions, significant nuclear abnormalities constitute the true precancerous pattern.

It is strange that so little is known about precancerous lesions leading to malignant lymphoma and leukemia. Mycosis fungoides not of the type described as *sarcome d'emblée* can be thought of as prelymphosarcomatous. Such a thing as a lymphadenoma may exist, but it must be extremely rare. I suppose that osteosclerotic anemia and polycythemia vera might be classed as preleukemic, hence precancerous, lesions. They constitute such a small segment of what must be the true basis of leukemia that they are scarcely worth mentioning.

Summary

If I can say anything in summary, it is that a pathologist can not describe something to the inexperienced individual and leave him with any notion of the groundwork for recognizing the precancerous state. To acquire this information, one must know lesion behavior from personal experience and that of others, and not merely the histologic appearance of tissues and cells. Lesions that even resemble cancer may well not be precancerous. Rather innocent-looking processes may, on the other hand, have serious import. One might wax Biblical and say, "By their fruits ye shall know them."

REFERENCES

1. Rider, J. A., Kirsner, J. B., Moeller, H. C. and Palmer, W. L.: Polyps of the colon and rectum. A four-year to nine-year follow-up study of 537 patients. J.A.M.A. 170:633-638 (June) 1959.
2. Rosenqvist, H., Öhrling, H., Lagercrantz, R. and Edling, N.: Ulcerative colitis and carcinoma coli. Lancet 1:906-908 (May) 1959.
3. Sternberg, S. S., Popper, H., Oser, B. L. and Oser, M.: Gall bladder and bile duct adenocarcinomas in dogs, following chronic feeding of Aramite. (Abstract.) Am. J. Path. 35:691-692 (May-June) 1959.

Lay Education in Cancer

E. CUYLER HAMMOND*

American Cancer Society, Inc., New York

E. CUYLER HAMMOND

ALTHOUGH precise data are lacking, there is abundant evidence that in the first two decades of this century very few cancer patients were cured, for the simple reason that few of them were treated until the disease had advanced to an incurable stage. This situation has been greatly altered for the better, due largely to successful educational programs of the American Society for the Control of Cancer and the American College of Surgeons. These programs were well under way in the 1920s.

Remarkable progress was made in a relatively short time. By 1935 to 1940 in Connecticut, the distribution of cases by stage of disease at time of treatment was 50 per cent stage I, 24 per cent stage II, and 18 per cent stage III (the remaining 8 per cent being unclassified as to stage). The over-all five year survival rate was about 25 per cent.

In the years that followed, further progress was made in improving the five year survival rate which rose to about 33 per cent and may be even higher than this at the present time. However, it appears that this latter improvement was largely attributable to better therapy. Except for cancer of a few sites such as the cervix, there was little change in the distribution of cases by stage of disease at time of first treatment.

The figures just quoted are for Connecticut, which was one of the first states to initiate an intensive cancer control program and the first to keep adequate statewide records on cancer incidence and survival rates. Comparable data are not available for the United States as a whole. However, it appears that the trend was similar throughout the nation, although some areas may have lagged behind by as much as a decade or more.

When any new and useful method is discovered, there is inevitably a lapse of time before it is fully utilized and maximum benefits are achieved. This is the time required for

*Director, Statistical Research Section, American Cancer Society, Inc., New York, New York.

the method to gain general acceptance and for the training of personnel. During this period progress may be very rapid. When it is finally accomplished, a plateau is reached. Further progress cannot be made until a still better method is found or until the old method is improved.

In respect to the early diagnosis of cancer, considerable improvement may now be made through the relatively new method of cytology. However, I am concerned here with the old and highly successful methods of lay education, namely, persuading people to have physical checkups and teaching the cancer danger signals. Available evidence suggests that with these we are rapidly approaching the plateau of maximum utilization. This is gratifying to the extent that it resulted from success. Considering this success, we should certainly not relax our efforts. However, to achieve further progress along these lines it seems to me that we will have to make substantial improvements in the old methods.

Now let us consider ways and means of doing so. First I will discuss the problem of periodic physical examinations.

Casting aside all practical considerations, maximum benefits might be achieved by giving thorough medical examinations, together with appropriate tests, to the entire adult population at frequent intervals. This is manifestly impossible at present. Assuming that a thorough examination takes about one hour of a doctor's time, it would require the full time of 258,000 doctors to examine everyone in the United States over the age of 25 four times a year. This exceeds the total number of physicians in the United States today. Even if the time were cut to 30 minutes per examination and the people were examined just once a year, the full time of about 32,000 doctors would be required. I suppose that this is in the realm of possibility and some day it may be put into actual practice. However, we are nowhere near it now. Even if put into effect, some people apparently free of cancer at the time of one such examination would have fairly advanced cancer before their next annual examination.

We are faced with two major difficulties: (1) the difficulty of persuading people to have periodic examinations, and (2) the limitation of medical personnel to give such examinations. I suggest that the first of these problems be met by preparing educational material with a more direct and personal appeal to selected groups of individuals, and that the second be met by concentrating our attention on high-risk groups.

A few examples will illustrate what I have in mind.

Instead of publicizing the half-truth that "cancer is no respecter of age or sex," I suggest that lay educators emphasize the fact that incidence rates of cancer of most sites vary greatly with age. Furthermore, some cancers which are common to both sexes occur more frequently in one sex than in the other.

While perhaps sad, it is nevertheless true that most people are far more interested in their own particular group than in mankind in general. This most human attitude can be turned to constructive purpose. Educational material should be prepared for and aimed at each specific age-sex group, special attention being given to those with the highest incidence rates of cancer. For example, material designed for men over 65 might well emphasize the high incidence of cancer of the prostate in this group. This information could be presented by radio and television during hours when retired people make up a large part of the audience.

In my opinion, material so designed and directed would have far more impact than a more general and diffuse approach. Let me illustrate this by a recent example.

Very recently, the newspapers published tables released by the Society of Actuaries showing relative mortality in relation to weight for each age-sex-height group. Like millions of other Americans, my wife and I quickly looked at the figures for our own particular categories. These concern us personally; these we will remember. Since then, smaller servings have appeared on my dinner plate.

Next, attention should be given to groups identified by such factors as geographic location, occupation, race, religion, etc. Incidence rates for cancer of specific sites vary consid-

erably from one such group to another. Educational material should be prepared and distributed accordingly. For example, in the South, attention should be called to the high rates of cancer of the skin and cancer of the cervix in that area. The cancer problem and the need to do something about it would thereby be brought closer to home for the people in the South.

By epidemiologic research we are learning of various environmental factors which are highly associated with the occurrence of cancer of specific sites. The major purpose of such studies is to ascertain the causes of cancer. However, the information can be put to good use whether or not causal relationships are established. For example, if it is true that cancer of the breast is excessively high among women who fail to breast-feed their children, then such women can be especially alerted to have more frequent checkups than might otherwise be necessary.

Now let us turn to the second part of the lay education program—teaching the cancer danger signals.

The danger signals have been designated as such because they are sometimes symptomatic of the presence of cancer. Unfortunately, these symptoms do not always occur before the disease has advanced to an incurable stage. Furthermore, the same symptoms may be produced by diseases or conditions other than cancer. Nevertheless, a very large proportion of all cancer patients come to the doctor because of a physical complaint (which is not necessarily one of the specified danger signals). This being so, the value of this aspect of the lay education program can hardly be doubted. The question is whether the program can be improved.

At this point I would like to propose a hypothesis: Conditions which, if long continued, eventually lead to cancer usually produce morphologic or physical changes before the occurrence of cancer. I will illustrate my point with three examples.

Factors which produce skin cancer after long exposure almost invariably produce at least minor changes in the skin years before the appearance of cancer. Lung cancer can be produced by prolonged exposure to certain dusts and shorter exposure to these same dusts produces lesions in the lungs and usually produces coughing. It is suspected that certain hormonal disturbances increase susceptibility to cancer, and such disturbances produce symptoms.

It is very likely that some patients with early cancer come to a doctor because of a danger signal or other complaint which was produced not by cancer but by the conditions which lead to cancer. If this be so, then we have a powerful additional tool for the detection of early cancer. To pursue this possibility, I think, a very thorough study should be made of physical complaints of all sorts in relation to the later occurrence of cancer. To be useful from the standpoint of lay education, such complaints would have to be recognizable by persons who have not yet seen their doctor about them.

This is one of the purposes of a large-scale prospective epidemiologic study which we are now getting under way. A large number of people are being asked to fill out questionnaires which include many questions about present physical complaints as well as past history of diseases. The subjects will be traced for six years to determine the later incidence of cancer among them.

No data from the main study are yet available. However, we have a little information on the prevalence of physical complaints as reported by 3,217 subjects over 30 years of age who filled out questionnaires a year ago when we were pretesting our procedures. About half of these subjects were enrolled by volunteer workers of the American Cancer Society in Baltimore, Harrisburg, Cleveland, Nashville and Tampa. The others were persons who answered questionnaires sent to them by mail. The latter group was selected from telephone books and city directories from many parts of the United States. About 58 per cent of them replied by the end of three mailings.

I wish to emphasize that the figures I am about to present are tentative and cannot be regarded as necessarily accurate. Much more extensive data will be available at a later date.

Figure 1 shows the percentage of people

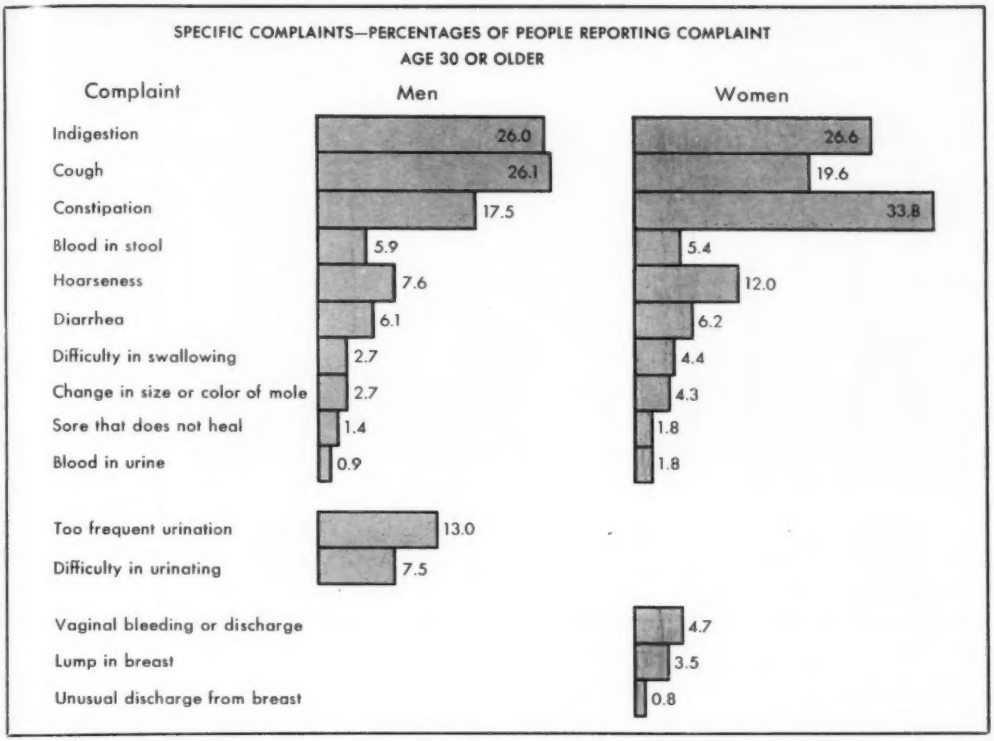


FIGURE 1.

who said that they currently had physical complaints of various sorts. Most of the designated cancer danger signals are included on this chart. Of those listed here, the most frequently reported were indigestion, cough and constipation. While constipation as such is not considered to be a danger signal, I think it not unlikely that severe chronic constipation over a period of many years may be related to the occurrence of cancer of the colon and rectum. There are 62.5 per cent of the subjects reported as having at least one of the complaints listed on the chart. Excluding constipation, diarrhea, too frequent urination, and difficulty in urinating, 49.7 per cent of the subjects reported that they had at least one of the other complaints listed, and 12.7 per cent said that they had two or more.

The subjects were asked whether they had seen a doctor in the last year concerning the complaints they had reported. Of those men who had reported a complaint which is regarded as a cancer danger signal, only 19.3 per cent had seen their doctor about it during the last year. The corresponding figure for women was 28.0 per cent. Clearly, the public has not yet been fully convinced of the need to see a doctor as soon as possible after the occurrence of a danger signal.

On the other hand, 58.4 per cent of the subjects said that they had visited a doctor during the last year.

I would like now to discuss the figures for each specific complaint, according to age, sex and severity of complaint.

Strangely enough, among men the percentage reporting indigestion decreased with age, while among women it was seen to be increasing with increasing years (figure 2). It will be interesting to learn whether this finding holds up when a larger sample is available for analysis. Of those who reported this com-

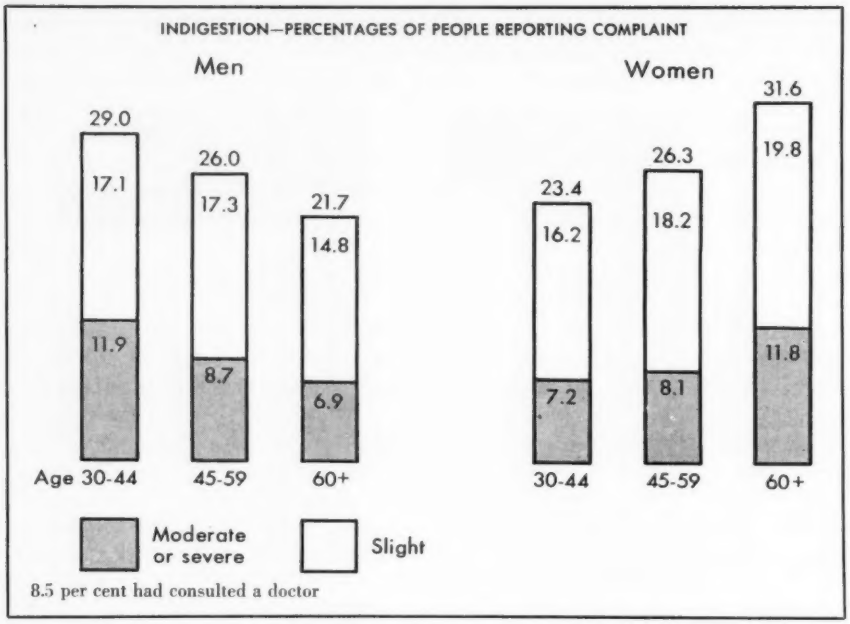


FIGURE 2.

plaint, roughly two-thirds indicated that they had slight indigestion and one-third that their indigestion was moderate or severe. Of those who complained of indigestion, 8.5 per cent had visited a doctor for it in the past year.

Among men the percentage reporting a cough increased with age, while the reverse was true among women (figure 3). Of these, 9.8 per cent had seen a doctor in connection with it in the last year. Sixty-nine per cent of those afflicted with cough reported that it had been with them for six months or longer.

Slight hoarseness is not uncommon, but there were few people who reported moderate or severe hoarseness (figure 4). This complaint was more common in women than in men.

Difficulty in swallowing is a relatively rare complaint (figure 5). It has been shown here on the same scale as that used for other complaints in order to illustrate this clearly.

Constipation, a common complaint, was reported far more frequently by women than by men (figure 6). Of those persons reporting this condition, 6.2 per cent had seen their doctor for it during the last year. Ninety-one per cent of those with constipation had been complaining of it for six months or longer. Only 6.4 per cent had experienced it for less than two weeks.

Diarrhea is relatively uncommon, but 12.6 per cent of those who suffered from it had seen a doctor within the last year (figure 7). Of the entire number reporting that complaint, 27 per cent indicated that it had been with them for less than two weeks.

Relatively few people stated that they had noticed blood in their stools often or fairly often (figure 8). More than half of this group reported that they had hemorrhoids.

Questions concerning urination were asked only of male subjects. As would be expected, the symptom of too frequent urination increased with age (figure 9). The complaint of difficulty in urination also increased with age (figure 10).

Other physical complaints relating to cancer danger signals were not reported in sufficient frequency to warrant showing figures by age and sex at this time.

Blood in urine appears to be an alarming symptom, since 30 per cent of those who had noticed it had seen their doctor for it in the

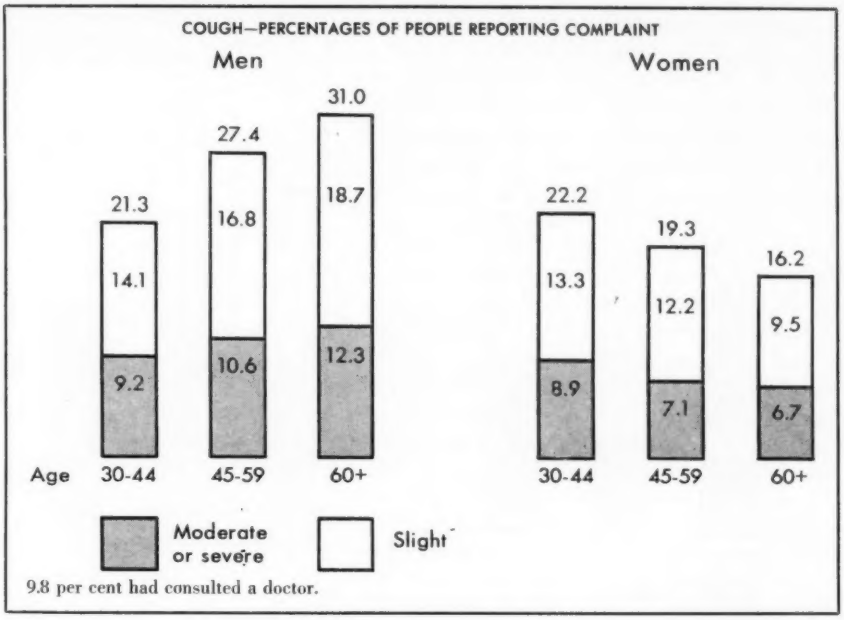


FIGURE 3.

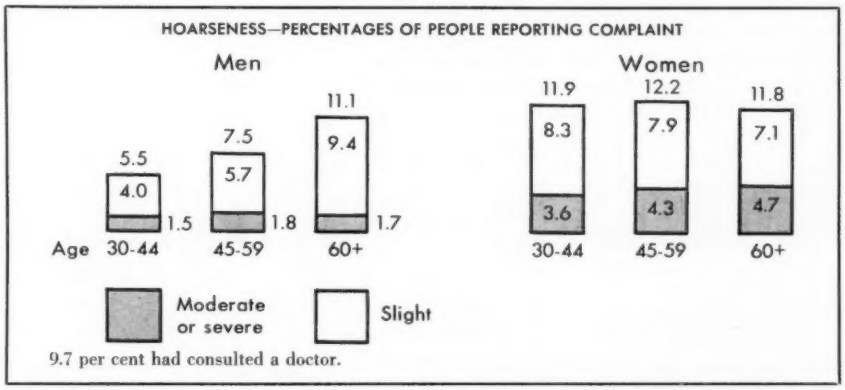


FIGURE 4.

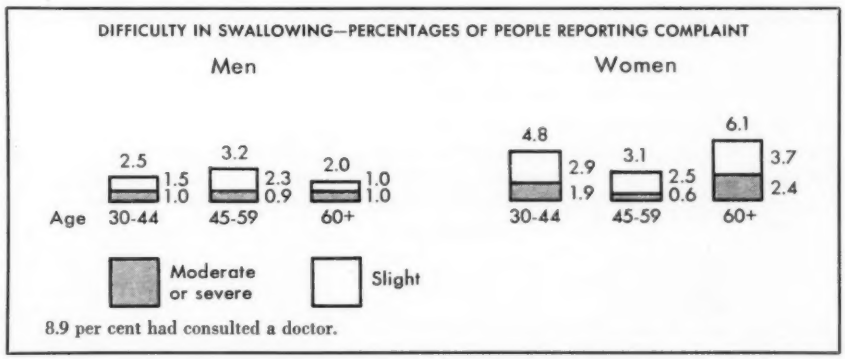


FIGURE 5.

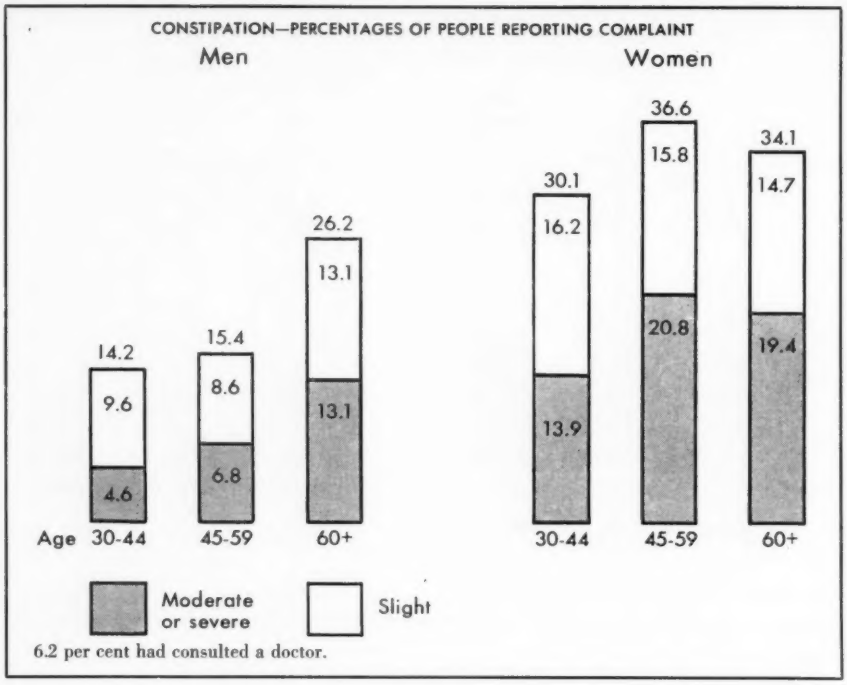


FIGURE 6.

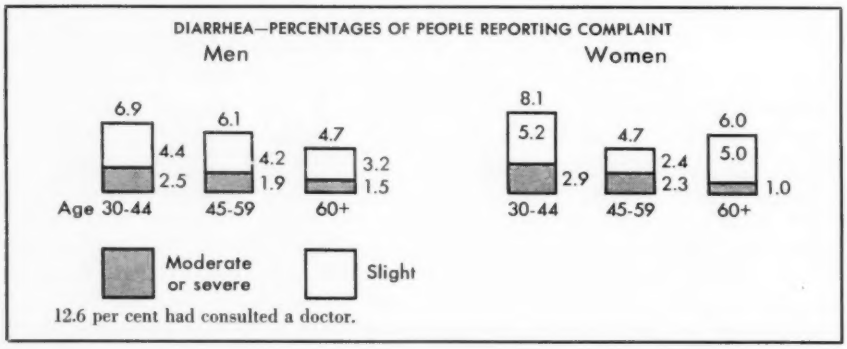


FIGURE 7.

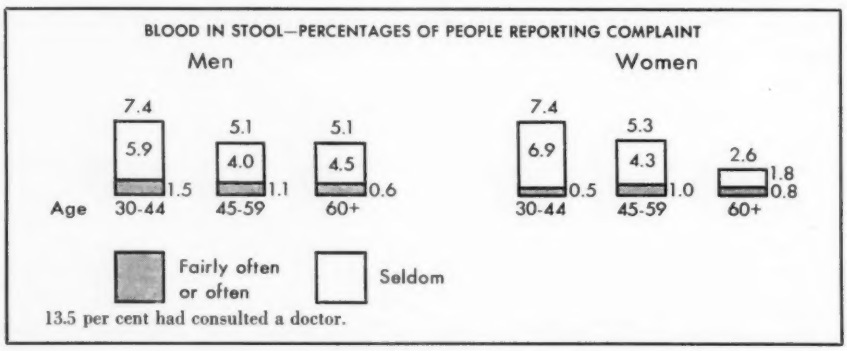


FIGURE 8.

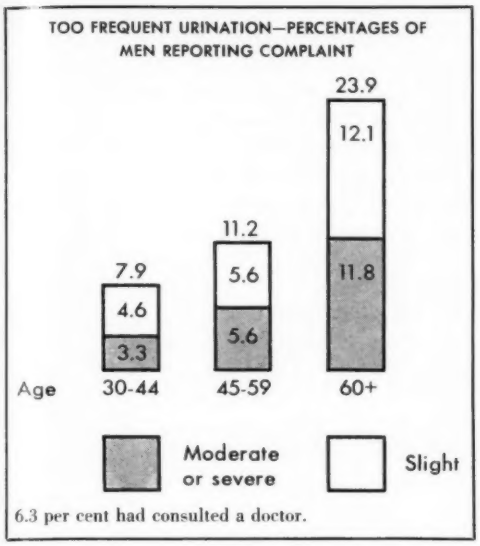


FIGURE 9.

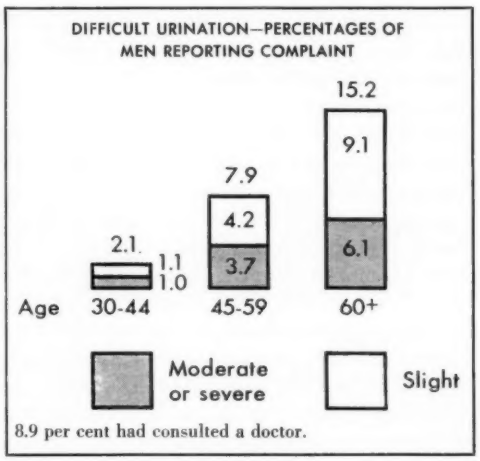


FIGURE 10.

last year. Of the few people who reported "a sore that does not heal," 36 per cent had been to their doctor.

Lump in breast was reported by 3.5 per cent of the women, and unusual discharge from breast was reported by 0.8 per cent. Slightly over half of the women who had noticed a lump in their breast informed us that they had seen a doctor about it. Although it was not the purpose of this study, the mere act of filling out the questionnaire may have induced many others to do so. The program to persuade women to examine their breasts appears to have been quite successful, since 41 per cent of the women said that they practice it every month.

I have shown figures only on physical complaints which are regarded as danger signals or are related to danger signals. Data are being collected on many other complaints. It is by no means impossible that among people with certain physical complaints, not at present thought to be related to cancer, the incidence of cancer may be much higher than among people free of these complaints. Data on this will be available in several years.

It is apparent that a very large proportion of all persons over 30 years old have, or think they have, one or more of the physical complaints which are listed as cancer danger signals. How frequently is an individual likely to see his doctor in connection with a complaint such as coughing which may have persisted for many years? I am afraid that he is likely to see his doctor once and, if he is assured that he does not have cancer, will consider that to be the end of his worries, at least as far as that particular complaint is concerned. This is a limitation on the value of the danger signals as now taught.

On the other hand, if it turns out that certain physical complaints identify groups of people with high incidence rates of cancer of specific sites, then it should be possible to persuade people with these complaints to have frequent medical checkups. In examining these people, special attention could be given to indicated sites, thereby increasing the chances of diagnosing very early cancer in these sites.

In closing, I must admit that I do not yet know whether the suggestions I have made will prove to be of practical significance. However, I believe that the possibilities are well worth investigating.

ACKNOWLEDGMENT

I would like to thank Mr. Lawrence Garfinkel for his assistance in preparing this paper.

Precancerous Lesions of the Breast; How to Treat Them

MURRAY M. COPELAND*

Georgetown University School of Medicine, Washington, D. C.

THE term "precancerous lesions of the breast" poses the question immediately as to the existing relationship between breast cancer and benign breast disease. The importance of determining this relationship is accentuated by the poor results now obtained in treating cancer of the breast. Not only is it necessary to appreciate the value of early diagnosis and adequate treatment; we must also be aware of predisposing factors and their relationship to the development of breast cancer.

MURRAY M. COPELAND

The term "benign breast disease" is an all-inclusive one under which a wide variety of tumors are classified. Breasts revealing the following benign entities are inclined to have a higher incidence of cancer associated with them than is noted among women in the general population whose breasts are not so affected: virginal hypertrophy, fibroadenoma, intracanalicular myxoma, giant myxoma, aberrant mammary tissue, intracystic papilloma, chronic lactation mastitis, and mammary dysplasia (chronic cystic mastitis). Many observers support a definite endocrine factor as being linked with mammary dysplasia,[1] benign mammary neoplasia,[2] and the production of carcinoma of the breast.[3,4]

The term "chronic cystic mastitis," inaccurate in its strictest sense, is applied to a group of benign breast lesions which are neither inflammatory nor truly neoplastic. The classification of the several forms of the disease has been much debated and includes a glossary of terms such as mammary dysplasia, fibrocystic disease, mastopathy, fibroadenosis, Reclus' disease,[5] sclerosing adenosis, Bloodgood's blue-domed cyst,[6] mazoplasia, mastodynia and others.

The abnormalities in mammary dysplasia have been regarded by numerous investigators as a probable basis for mammary carcinoma. The list of authors is a long one and includes such names as Cooper,[7] Billroth,[8] Aschoff,[9]

*Professor of Oncology, Georgetown University School of Medicine, Washington, D. C.

Ewing,[10] Konjetzny,[11] MacCarty and Mensing,[12] Semb[13] and others. Schimmelbusch,[14,15] in 1892, stated that in three of 43 patients with *Cystadenom* cancer of the breast subsequently developed. Rodman[16] found cancer associated with chronic cystic mastitis in 15.5 per cent of 100 cases. Cheatle and Cutler[17] observed that approximately 20 per cent of all mammary cancers have their onset in the changes of chronic cystic mastitis.

Two important studies led to opposing conclusions. Campbell,[18] in 1934, reporting on 290 cases with simple cystic disease and adenocystic disease, showed that such changes were not significantly related to cancer. Warren,[19] in 1940, concluded that patients with chronic cystic mastitis showed a predisposition to mammary cancer. Other investigators have reported more or less confirmatory clinical data, some of which are difficult to assess because of the confusing terms used in describing the disease.

It is of paramount importance that terms expressing the dominant features of a pathologic picture be used in statistical reporting of the various breast entities. Earlier studies of the relationship between benign breast disease and cancer were sometimes speculative and primarily descriptive. More recent investigations have been based upon clinical (statistical) and histologic (microscopic) proof and animal experimentation.

Clinical Data

At present, the most reliable method of determining the tendency of cancer to supervene in the various forms of mammary dysplasia is to follow a large group of cases for a sufficient number of years.

A total of 3,247 cases of benign diseases of the breast from the clinic and surgical pathologic laboratory of the late Dr. Joseph Colt Bloodgood[20] in Baltimore, and from the Oncology Department of the Georgetown University Hospital in Washington, D.C., have been analyzed. Nine hundred and thirty-six cases with mammary dysplasia, 256 with fibroadenoma, and 119 with intracystic papilloma have been followed for an average of approximately 10 years. The incidence of mammary cancer in the 936 cases of mammary dysplasia was 1.35 per cent rather than the "normal" expected incidence for women with cancer in the same age group. This indicates the development of cancer at about three times the expected rate. Those patients showing proliferative changes (adenosis of the breast) had the greatest increase in cancer incidence—approximately seven times the expected rate (3 per cent). In 256 cases with fibroadenoma, breast cancer developed in two patients, or approximately twice the expected rate. Among 119 cases of benign breast papilloma, only 57 had local excision for removal of the lesions. Three patients of this latter group subsequently developed cancer in the same breast.

These over-all results are in reasonable accord with the reports of Lewison in Baltimore,[21-23] Warren in Boston,[19] Clagett and associates at the Mayo Clinic,[24] and others.[25] Specifically, Lewison found that the breast cancer incidence in pre-existing benign breast conditions was 2.6 to 3.6 times as great as expected. Warren's report indicated an incidence of cancer 4.5 times as great as expected; and Clagett's series showed an incidence five times greater than expected. All of these studies represent a similar trend in statistical findings, indicating increased incidence of cancer in breasts which had been the site of dysplasia or benign neoplasia.

Foote and Stewart[26] feel that follow-up studies, so far, have not produced conclusive evidence that any specific lesion or lesions associated with so-called chronic cystic mastitis are "particularly apt" to be followed by cancer. They feel that the soundest statistical studies do point to some positive relationship.

Microscopic Data

Microscopic proof of a direct relationship between benign breast conditions and breast cancer should offer a simple and direct way of solving this as yet incompletely solved relationship. Microscopic changes resembling those seen in mammary dysplasia are relatively common in breasts removed for cancer. The incidence of such changes has been reported by various investigators as being between 20 per cent and 50 per cent. Such findings have

been put forward as an indication that cancer may arise from such abnormalities in the mammary gland.

Mammary tissue removed at autopsy from women in the cancer age group, without clinical evidence of cancer or mammary dysplasia, has also shown histologic changes similar to those seen in breast dysplasia. Borchardt and Jaffe,[27] in 1932, observed at autopsy atypical involution, microscopically similar to mammary dysplasia, in the breasts of 93 out of 100 women over 40 years of age. This material was obtained from individuals who had been free from specific breast symptoms. Franzas,[28] in 1935, observed histologically similar changes in 55 per cent of 100 women without clinical evidence of breast changes. Geschickter[20] studied the breasts of 100 women with clinically normal breasts at autopsy. He observed lobular irregularities and cystic dilatation of ducts in 33 per cent of women between 30 and 40 years of age. In women between 40 and 50 years of age, somewhat similar findings—but with cystic changes predominating—were noted in 50 per cent of the cases. More recently Frantz and her colleagues[29] found the frequency of latent breast abnormality to be high (53 per cent) in a special study of the breasts of women in 225 routine autopsy cases.

Histologic studies made on human breast tissue cannot be cited as convincing evidence of the transition of hyperplasia or involutional dysplasia into malignancy so long as morphologic criteria are lacking to distinguish between benign neoplasm and early malignant change. Pathologists vary in the criteria on which they rely to make a diagnosis of early cancer, and, certainly, none of the criteria are infallible. Foote and Stewart[26] feel that a better proof of causal relationship depends on showing a direct anatomic association. This, of course, greatly reduces the number of ideal lesions for study, and, in general, very few pathologists have reported specific instances that show convincing transition forms which fulfill the guide lines laid down for the identification of noninfiltrating cancer. Foote and Stewart[26] stated that they have seen cancer begin in duct papillomatosis, solitary and multiple cysts, apocrine epithelium, and blunt duct adenosis, although they are unable to give precise figures. In Geschickter's[20] observations on this subject he noted that in the study of 90 sections of small mammary cancers (1.5 cm. or less in size) the majority of the tumors had their origin within areas of atrophy and fibrosis, in a region where small fibroadenomatous nodules were present, or within lobules undergoing atrophic and secretory changes. In six cases (6.6 per cent) the histologic picture suggested that the cancer arose in an area of mammary dysplasia.

Louis[30] and also Lewison[23] have both suggested the possibility of a differential stain attack on the problem of distinguishing between benign epithelial hyperplasia and malignant epithelial neoplasia. Fluorescent staining has been used by Louis with considerable success. This, of course, has not answered the burning question of relationship between the benign breast lesion and breast cancer; however, it may serve to further clarify the probability of its occurrence.

Experimental Data

Since 1930, considerable animal experimentation has been carried out in the production of cystic and proliferative changes, as well as of cancer, in the breasts of rats and mice. It has been possible to produce mammary cancer in mice and rats by large and prolonged dosages of estrogen. The classic work of Lacassagne[31-35] indicated that changes characteristic of chronic cystic mastitis were often an essential precursor of mammary carcinoma, which was produced in response to the estrogenic hormone.

Geschickter, Lewis and Hartman,[36] in 1934, produced cancer in the rat's breast by a variety of methods of overdosage of estrogen. They noted two essential features of the experiments. First, mammary cancer is not necessarily preceded by cystic and hyperplastic changes characteristic of mammary dysplasia. Second, when such changes do precede the development of mammary cancer, a continued estrogenic stimulation must intervene. Since that time estrogenic hormones in a variety of chemical forms have been administered in

high and prolonged doses to mice, rats, guinea pigs, rabbits, dogs, monkeys and other laboratory animals by a number of investigators and their associates,[37] including Burrows,[38-42] Goormaghtigh,[43] Goormaghtigh and Amerlinck,[44] and Van Wagenen and Gardner.[45] Despite the fact that more than two decades have passed, the riddle of cancer has not been solved by attempting to trace its development under the stimulation of hormonal substances. No one has succeeded in producing the cellular transformation from the benign to the malignant state by using a single chemical compound or a group of such compounds. Engle, Krakower and Haagensen,[46] in 1943, reported on the results of intensive and sustained estrogenic administration to mature female monkeys. The morphologic benign changes in the endometrium far overshadowed any of the findings described in the breast tissue.

Geschickter and Hartman[47] recently (1959) reported on mammary response to prolonged estrogenic stimulation in the monkey. They concluded that there is no evidence that estrogenic treatment in extremely high dosages, over periods of as long as seven years and seven months, has produced malignant changes in the mammary glands of monkeys. In general, all the monkeys studied received similar treatment. They were injected every day with 1 cc. of estrone (10,000 I.U. per cubic centimeter), or estradiol (30,000 rat units per cubic centimeter). In addition, each week two pellets of estrone, 3 mg. each, were implanted subcutaneously. Some received estradiol pellets and, in addition, some received 800 mg. of estradiol powder under the skin at the start of the experiment.

That mammary enlargement can occur in both male and female human subjects in response to estrogen is attested to by many observations. Infantile hypertrophy is noted in young girls with granulosa cell tumors of the ovary. Gynecomastia is noted in men with infectious hepatitis where the liver fails to metabolize estrogens. It also is noted in men who work in laboratories in which estrogens are processed. Small girls in whom gonorrheal vaginitis is treated by estrogens will show breast hypertrophy.

Clinically there is much to suggest that chronic cystic mastitis is hormone-responsive and probably is brought about by an imbalance between the estrogen and progesterone hormonal complexes. The cystic and proliferative changes produced in experimental animals in response to abnormal hormonal environment are similar to those seen in human chronic cystic mastitis. There is, of course, due reason for caution in prognosticating the production of breast disease and cancer, or lack of it, from one species to another. In the human, Geschickter[20] has shown that a form of mammary dysplasia—adenosis—is related to a relative hyperestrinism in premenopausal women. Three per cent of patients with such lesions have a complicating breast carcinoma.

The relationship of estrogens to precancerous and malignant changes in the mammary gland of humans is difficult to prove.[3] There are four reports in the literature[48] on breast cancers which were recognized during or shortly after the administration of estrogen therapy. Foote and Stewart, after an analysis of their own five cases and of three recorded cases in the literature, felt that they could not enter into a critical discussion of the cases. One major reason for taking this position was lack of accurate knowledge of the histologic structural changes in the human female breast following treatment with estrogenic hormones. Such descriptions are rare at present. Judged by the few cases available for study, Foote and Stewart[26] stated that no sequence of changes beginning with a normal breast and ending with breast cancer had been encountered. In most instances, estrogen had produced no noteworthy specific alterations in the breast structure. Furthermore, attempts to trace such changes experimentally in rhesus monkeys have met with failure.

There can be scarcely any doubt, however, that estrogens are directly concerned in the development and progress of certain human breast cancers. Observation of patients with advanced breast cancer has shown that a considerable number of the tumors are estrogen-stimulated. Alteration of endocrine environment by means of castration, other endocrine ablative procedures, or by giving antagonistic

sex steroids is therapeutically beneficial in the endocrine target-sensitive human breast cancers (approximately 45 per cent). This further substantiates a close estrogen relationship to breast cancer.

Discussion

From the foregoing findings and results it would seem safe to assume that there does exist a basic relationship between breast cancer and benign breast disease. The clinical statistics appear the most impressive; the histologic evidence is, to a degree, substantive; and the experimental evidence definitely correlates breast dysplasia with cancer in animals and strongly suggests that a basic endocrine environment is present and necessary in the development of human mammary dysplasia (chronic cystic mastitis) and in a number of breast cancers.

The following observations are cited in support of the causal relationship between benign breast lesions and cancer: (1) In many cases, breasts removed for cancer show the changes of some form of chronic cystic mastitis (breast dysplasia) or an occasional relationship of cancer to a pre-existing fibroadenoma or papilloma; (2) transitional stages between breast dysplasia and carcinoma have been traced by some investigators; (3) while experimental production of mammary cancer following cystic disease and adenosis is not possible in the higher order of Mammalia to date, it has been accomplished in rats and mice by using estrogenic hormones; (4) among patients treated conservatively for mammary dysplasia, a number have developed mammary cancer subsequently (3 per cent).

Treatment

In the belief that certain benign breast lesions reflect changes in the breast which may lead to cancer, it becomes important to recommend that all patients with benign breast disease be examined at periodic intervals. Surgical treatment, in the form of either aspiration of a cyst or the excision of nodular tissue, is indicated whenever there is the slightest suspicion that mammary cancer may be present. Aspiration of a cyst suffices to establish the diagnosis in most cases of cystic disease. For solid tumors and questionable areas of nodulation or cysts, excision is the treatment of choice. A complete and careful excision of a small tumor (up to 3 cm. in diameter) for frozen section is a recommended procedure. The pathologist is thus provided with an adequate specimen for study. Incisional biopsy is employed in larger tumors (4 cm. or more in diameter).

In the case of discharge from the nipple, without evidence of palpable tumor, a Papanicolaou smear should be done to establish the presence of red blood cells. If localization of the bleeding lesion can be accomplished, the duct system in the area should be excised. This may necessitate doing a quadrant resection. Further definitive treatment should be based on frozen section at the time of operation. For bleeding or serosanguineous discharge from the nipple, without evidence of site localization, the patient should be kept under close observation with frequent Papanicolaou smears, if premenopausal. In the postmenopausal state, the likelihood of carcinoma of the breast as a cause of bleeding from the nipple increases with age. Persistent bleeding without satisfactory evidence for cause justifies simple mastectomy.

Because of space limitations, the list of references has been omitted here but is included in the author's reprints and is also available on request to the Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

Recognition and Management of the Cutaneous Precanceroses

FRANCIS W. LYNCH*

University of Minnesota Medical School, Minneapolis

FRANCIS W. LYNCH

By this stage of the symposium the concept of a precancerous lesion has already been explored and defined by others. Although there may be differences of opinion as to an exact meaning for the term precancerous lesion, the important point is the significance of the concept that certain recognizable cutaneous lesions are forerunners of cancer so frequently that their destruction or removal is a valuable prophylactic procedure. The public should be informed of this concept, and the profession should be made so familiar with all such lesions that cancer may not be allowed to develop unnecessarily. The morphology, classification and management of such cutaneous precanceroses will be dealt with in this paper.

As regards the term precancerous lesion, the prefix pre- can refer to something occurring prior to another condition or to an early stage of a condition; the concept of -cancerous is clear and applies equally to lesions only locally malignant or to those capable of metastasis. A lesion is a localized morbid structural change. Application of the broader term precancerosis calls attention to certain precancerous processes which (1) are more diffuse than circumscribed, (2) need be no more morbid than is aging—which is life itself—and (3) may be more biochemical than structural in nature.

Classification

The list of cutaneous precanceroses is long, but it can be divided according to extent, nature, rate of progress in malignancy and frequency (table 1).

Senile keratosis is a prototype of cutaneous precancerosis, occurring with great frequency and probably obligated to transform to cancer, most likely to be squamous cell in type, though often this transformation would require a period beyond the span of a human lifetime, as we now know it. Some of Blum's

*Professor and Director, Division of Dermatology, University of Minnesota Medical School, Minneapolis, Minnesota.

TABLE 1

CUTANEOUS PRECANCEROSES

- Circumscribed precancerous lesions
  - Epithelial
    - Hyperkeratoses (probably obligate)
      - Senile (type) keratosis (figures 1 to 4)
        - Natural
        - Artificial
          - Xeroderma pigmentosum
          - Irradiations
          - Tars and hydrocarbons
          - Arsenic (figure 5)
      - Cutaneous horn (figure 6)
      - Leukoplakia
        - Oral
        - Genital
    - Other warty lesions (frequent precursors) (figures 7 to 12)
      - On abnormal skin (e.g., xeroderma pigmentosum and radiodermatitis)
      - Condyloma (verruca) acuminatum (?)
    - Epithelial nevi (occasional)
      - Nonverrucous
        - Benign basal-cell epitheliomas
          - Simple, nonadenoid, with or without pigment (figures 13-16)
          - Follicular-trichoepithelioma, sebaceous adenoma (figure 17)
          - Hidrocystadenoma
          - Cylindroma (turban tumor)
      - Verrucous
        - Linear epithelial nevus
        - Nevus syringocystadenosus papilliferus (figure 18)
      - Pigmented, keratotic
        - Early in life (figure 19)
        - Seborrheic keratoses ("senile warts") (figures 20, 21)
      - Cysts
        - Sebaceous
        - Epidermoid
    - Intra-epidermal proliferation (slowly progressive epithelioma)
      - Dyskeratotic
        - Pagetoid change
        - Bowen's disease (figure 22)
        - Erythroplasia of Queyrat (figure 23)
        - Borst-Jadassohn epithelioma
      - Basal-cell type
        - Superficial "benign" epitheliomatosis (figure 24)
  - Melanocytic
    - Junctional nevus
    - Compound nevus with junctional activity
    - Lentigo maligna (slowly progressive melanoma) (figures 25, 26)
  - Dermal
    - Fibroma (as in neurofibromatosis)
  - Rarely precancerous
    - Infection: syphilis, lupus vulgaris, etc.
    - Inflammation: margin of chronic ulcer
    - Dermatosis
      - Lichen sclerosus et atrophicus
        - Kraurosis vulvae
        - Balanitis xerotica obliterans
      - Psoriasis (?)
    - Scar: following burn
- Diffuse precancerous changes
  - Following natural ultraviolet and perhaps other atmospheric radiations in:
    - Red-haired, blue-eyed, freckled persons, especially
    - Xeroderma pigmentosum
  - Following artificial irradiation by:
    - Heat (erythema ab igne)
    - Ultraviolet rays
    - Other atmospheric rays (?)
    - X-rays
    - Radium or other radioactive elements
  - After tars or hydrocarbons
  - After administration of arsenic

experimental studies suggest that even minimal actinic exposure initiates irreversible progress toward malignancy, although the rate of progress depends on cumulative effects of exposures. The activating cause of keratoses is radiation, and there is direct relation to inheritance and to amount and nature of the exposure to radiation. Dark and seborrheic skin carries but slight proclivity. Strong association rests with blond skin, freckling tendency, and the associated inheritance of red hair and blue eyes; racial factors are therefore clearly evident. While the nature of the inheritance is not yet clear, it is likely to be both structural and functional, anatomic and biochemical, and is to be regarded as natural rather than morbid. Morbidity is clearly evident in the inherited trait of hypersusceptibility as seen in xeroderma pigmentosum, which is too rare to deserve more than mere mention in this paper.

A wide range of radiation bands is capable of producing and activating keratoses: sunlight, perhaps other atmospheric ionizing phenomena, artificially induced ultraviolet rays, x-rays, and the emanations of radium and related elements. Exposure to natural irradiation is strongly influenced by habitat (proximity to the equator, altitude, and atmospheric moisture content), as well as by social habits

FIGURE 1. Senile (type) keratosis in young person.

FIGURE 2. "Active" senile keratosis undergoing a change to cancer.

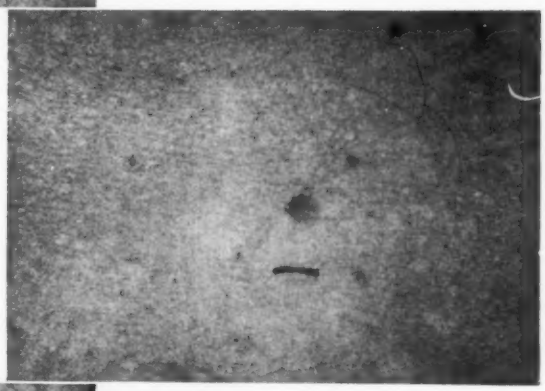


FIGURE 3. Senile keratosis occurs less frequently on the trunk.

FIGURE 4. Senile keratosis having transformed to cancer (compare appearance with keratoacanthoma).

FIGURE 5. Arsenical keratoses.

FIGURE 6. Cutaneous horn with suspicious base.

FIGURES 7, 8 and 9. Keratoacanthoma. In spite of the resemblance to squamous cell cancer, all of these keratotic lesions are benign and not even precancerous.

FIGURE 10. Xeroderma pigmentosum —precancerous.

FIGURE 11. Xeroderma pigmentosum after the development of cancer.

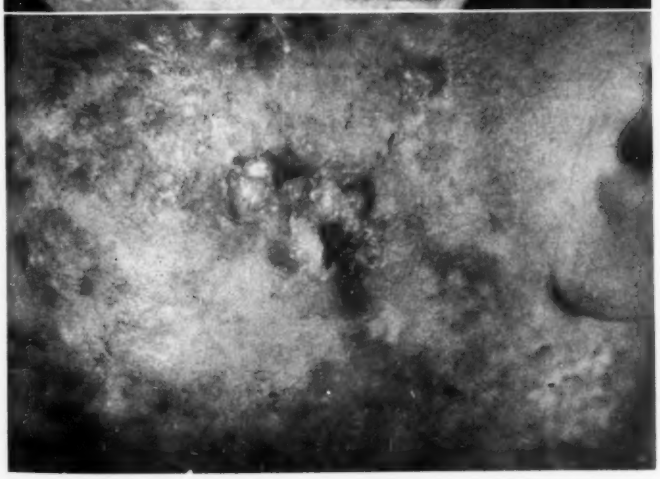


FIGURE 12. Radiodermatitis after progression to cancer.

FIGURE 13. Basal-cell epitheliomas which have developed from lesions which earlier appeared histologically to be benign.

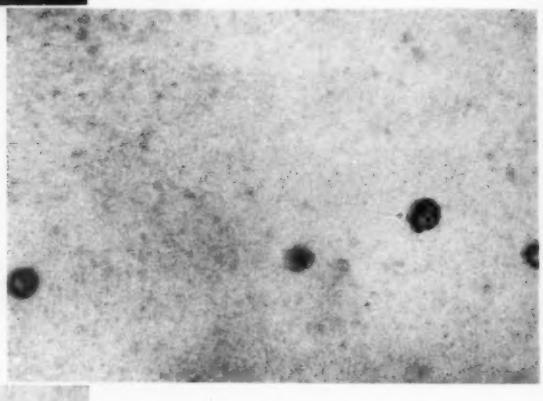


FIGURE 14. Pigmented basal-cell epitheliomas: Appearance is clinically and histologically benign.

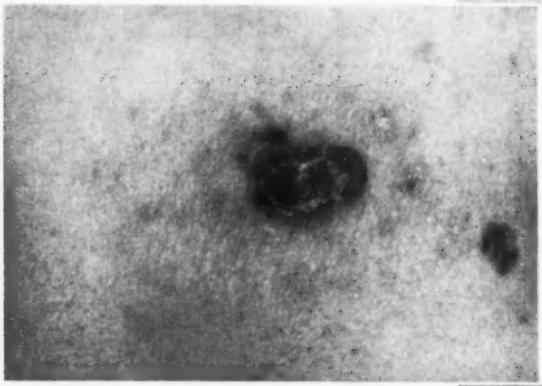


FIGURE 15. Pigmented basal-cell epitheliomas: later stage in same patient with malignant transformation.

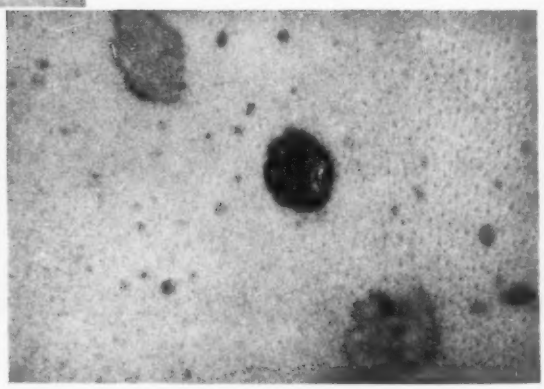


FIGURE 16. Superficial (and only slightly pigmented) basal-cell epitheliomatosis is present in close relation with apparently benign ("nevoid") pigmented epithelioma in the same patient.

FIGURE 17. Trichoepithelioma: A basal-cell epithelioma which usually remains benign.

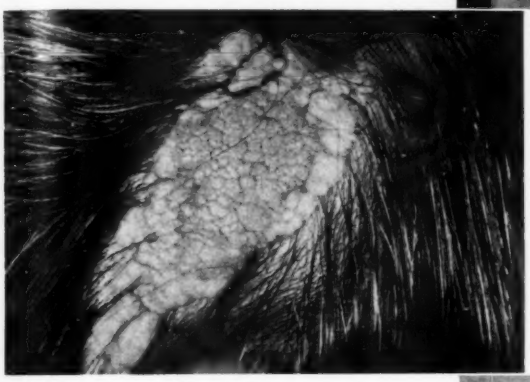


FIGURE 18. Nevus syringocystadenosus papilliferus: An epithelial nevus which occasionally may become a basal-cell epithelioma.

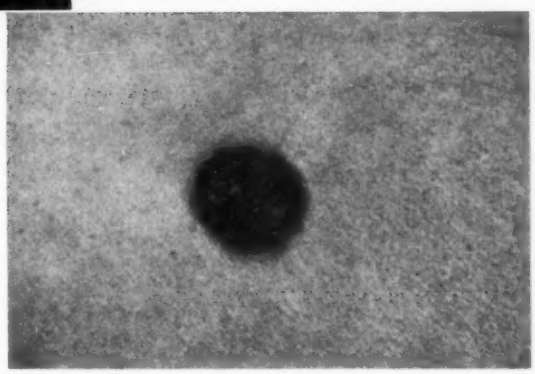
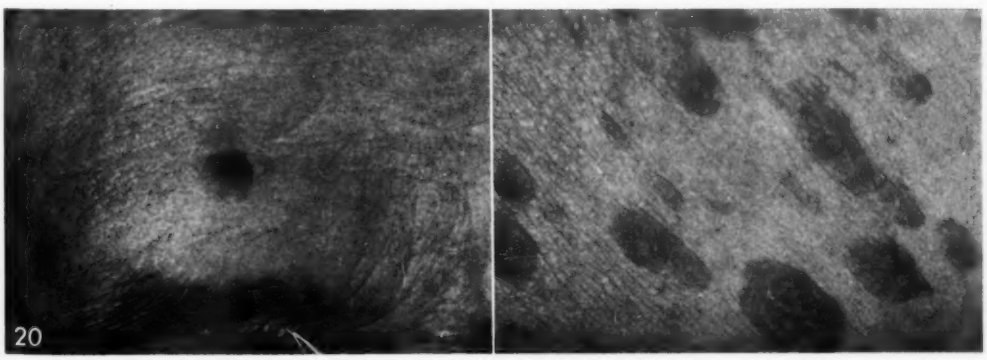
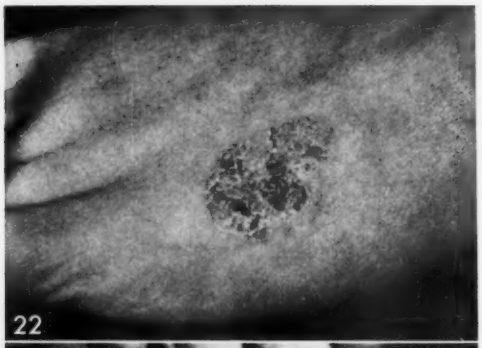


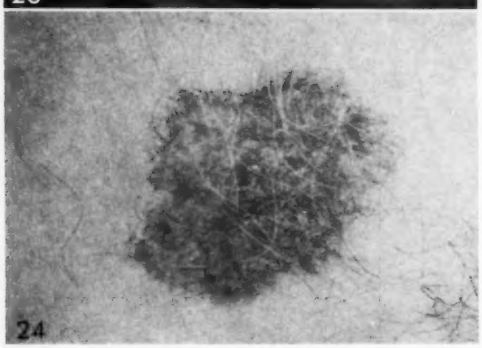
FIGURE 19. Pigmented epithelial nevus. Clinically and histologically similar to seborrheic keratoses, these lesions are more obviously nevoid and occur early.

FIGURES 20 and 21. Seborrheic keratoses ("senile warts"). These are benign and rarely become cancerous.



20





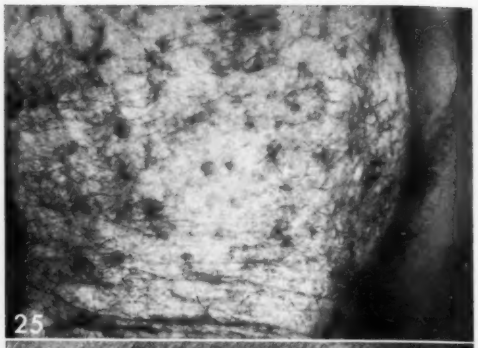


FIGURE 22. Bowen's disease.

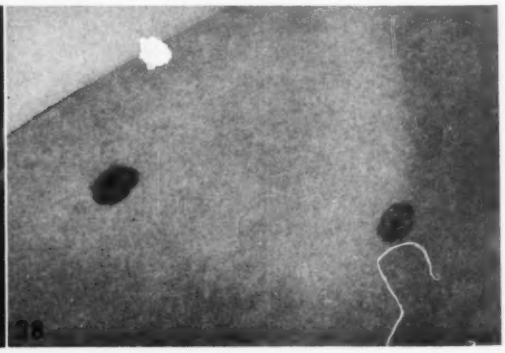
FIGURE 23. Erythroplasia.

FIGURE 24. Superficial epitheliomatosis. Although often listed as precancerous, these lesions are intra-epidermal epitheliomas ("cancer *in situ*").

FIGURE 25. Lentigines. Pigmentary changes occurring in senile precancerous skin.

FIGURE 26. Lentigo. These larger lesions can become malignant melanomas.

FIGURES 27 and 28. Common moles on face and trunk which are benign but enter into differential diagnosis of precancer and cancer.



(clothing, leisure, deliberate exposure) and by occupational factors (for example, in sailors, farmers, ranchers). Other external factors can predispose or even produce keratoses: application of tars and certain hydrocarbons, apparently by direct action as well as by increasing susceptibility to the action of radiations. There is no clear idea as to the manner in which arsenic produces keratoses and epitheliomas by internal action, although when externally applied, its cauterizing action can produce chronic ulcers and thereby lead to cancer.

A keratosis occurs more frequently on visibly atrophic skin and may develop on skin which appears grossly to be normal. The earliest apparent change may be in color (red, gray, yellow-brown) or texture (visible scale or palpable thickening). The rate of growth is unpredictable but slow, and the change to cancer generally requires years, although several months can suffice. The warning of imminent or actual malignant change may be an increased rate of growth, especially in thickness, or the development of signs of inflammation or the development of ulceration.

The cutaneous horn is a variant of senile keratosis, projecting like a filiform wart but with harder, horny scale distally and with a distinct base evident as a very narrow and only slightly elevated band. The rate of growth and frequency of malignant change is greater than in the common keratosis.

Leukoplakia is to a considerable extent a mucosal counterpart of senile keratosis. It is considered elsewhere in this symposium.

On senile skin or in xeroderma pigmentosum or radiodermatitis, one may observe warty lesions seemingly different from both warts and keratoses, but potentially malignant. Their nature is not entirely clear.

There is question whether the common wart can become a cancer. The few reported instances relate principally to condylomas under a phimotic prepuce and could be interpreted as the result of chronic infection, inflammation or irritation in a predisposed area rather than as a direct transformation of the virally produced benign tumor, the wart.

Verrucous and nonverrucous, pigmented or nonpigmented epithelial nevi do not often become malignant. Particularly the nonverrucous lesions provide a wide range of type—true nevi, nevoid epitheliomas and benign epitheliomas—and the prognosis in a given case may not be evident clinically or microscopically until the lesion has been observed for a considerable period. Both these lesions and sebaceous cysts usually transform to basal-cell carcinoma if a malignant change occurs.

Intra-epidermal epitheliomas of the various types may grow very slowly for a long period and then, for no apparent reason, become more active and invasive. They probably should not be classed as precancerous at any stage, not even their earliest.

The melanocytic precancerous lesions are reviewed elsewhere in this symposium and are mentioned here only because it may be difficult clinically to distinguish them from some larger but nonelevated senile or seborrheic keratoses. In certain instances, early senile keratoses and senile lentigines may be difficult to identify even under the microscope.

There are very few presarcomatous cutaneous lesions, although in some forms of sarcoma only slight malignant tendency may be noted in their early stages. Sarcomatous change does occur occasionally in some of the larger lesions in cases of neurofibromatosis.

In the past, there has been accusation of considerable precancerous tendency toward squamous-cell carcinoma in certain infections and chronic ulcers, but retrospection suggests that many such opinions were based on the misinterpretation of pseudoepitheliomatous processes.

Kraurosis vulvae seu penis is overly feared as a precancerosis. In this disorder a change toward malignancy occurs only when leukoplakia supervenes and transforms the lesion.

Carcinoma occurs occasionally in larger scars following burns from heat and has been observed in erythema ab igne.

Because of the high frequency of progressive change, the diffuse processes listed in table 1 are regarded as precancerous even before the development of localized keratoses, other warty lesions, hyperpigmented macules or ulcers in these areas.

TABLE 2

DERMATOSES ASSOCIATED WITH INTERNAL CANCER

Bowen's disease (?)
Dermatomyositis
Acanthosis nigricans
Sturge-Weber type of facial hemangioma
Syndromes associated with endocrine tumors
Carcinoid syndrome
Cutaneous metastases from within
Cutaneous involvement by extension
Eruptions associated with lymphomas and reticuloses
Specific infiltrations
Nonspecific involvement: pruritus; purpura; urticaria; eczematous, vesicular or bullous eruptions, and severe or generalized herpes zoster

Although not proved to be precancerous, the eruptions listed in table 2 are somehow associated with internal processes of a malignant nature and deserve mention here because they should stir the clinician to a serious search for internal cancer in patients bearing these eruptions.

Diagnosis

Precancerous lesions are to be differentiated from certain benign conditions on one side and early cancer on the other. Senile keratoses and other small warty lesions of a precancerous nature seldom appear early in life and can usually be recognized by their characteristic appearance and the fact that the surrounding skin shows the atrophic changes of senility or other abnormal state. There is no sharp line dividing such lesions from early cancer. The warning signs of increased rate of growth, rapid hyperpigmentation, increased scaling, inflammatory change, fissures, ulcer, bleeding, etc., are observed both before and after there is microscopic evidence sufficient for the recognition of cancer. Such lesions must also be distinguished from some which are unrelated to cancer, such as warts, keratoacanthomas, etc.

The epitheliomatous nevi present greater diagnostic difficulty and one may not always have definite warning of danger. Early in life there may be no definite features distinguishing benign from potentially malignant lesions. Progressive growth may then be the only premonitory evidence. One also becomes suspicious in later years if there is reactivation of growth, although superficial ulceration often is the first apparent change. The "common mole" can usually be distinguished by being less firm, but it can be hard and then may be indistinguishable grossly from epitheliomatous nevi or epitheliomas, benign or malignant. Cysts are suspect only after becoming inflamed or ulcerated or developing a renewed tendency toward growth.

Rarely do physicians other than dermatologists recognize clinically the true character of the intra-epitheliomatous malignancies which often resemble dermatitis or psoriasis. One needs a high index of suspicion and careful visual examination of such lesions.

The Role of Biopsy

Because of the frequent incidence of precancerous lesions, their tendency toward multiplicity, their occurrence on exposed surfaces, etc., it is obviously impractical to recommend removal of all such lesions. A decision to treat is based on progressive enlargement or other suspicious change, concern on the part of the patient unrelieved by sound professional advice, or such location, limited number or size of lesions as to make their removal a relatively simple procedure. Biopsy need not be considered in early stages of the hyperkeratotic lesions. Many authors have expressed the view that the removal of any hyperpigmented lesion should be accompanied by biopsy; this is impractical and unnecessarily expensive. A physician incapable of recognizing the indications for biopsy should not remove such a lesion, but should arrange for consultation. Hyperkeratotic or hyperpigmented lesions require biopsy only if they are enlarging or show the aforementioned signs suggesting a malignant tendency.

For proper interpretation of changes observed in cutaneous lesions, the pathologist, whether general or dermatologic, deserves adequate clinical information, that is, a brief history and description and the age of the patient. This is particularly true with pigmented lesions and in cases where pseudoepitheliomatous reaction might be present. It is clearly evident that in many cutaneous lesions and

conditions there is considerable diagnostic advantage on the side of the dermatologist who is capable as a clinician and histopathologist.

In cases of suspected lesions one usually may best perform biopsy with the curved blade of a scalpel or with the circular blade of the cutaneous biopsy punch, followed by electrosurgical removal of the remainder of the lesion. In some instances, as in lesions larger than 1 cm. in diameter or enlarging pigmented lesions, it may be preferable to excise the entire lesion and submit all or a suitable portion for pathologic study.

Logic might appear to suggest that biopsy would be more frequently used by the less experienced clinician, but in actuality the more capable, better-trained clinician of greater experience is more likely to utilize this valuable diagnostic aid.

Treatment

Having established a diagnosis of a particular type of precancerosis—not just vaguely suspecting a "precancerous lesion"—one comes to consideration of management. Not every precancerous lesion must be removed. An estimate of rate of growth and progress toward malignancy can sometimes lead a conservative clinician to restraint; very numerous lesions, advanced age, a serious disease, or poor general health may justify a period of further observation with subsequent periodic re-evaluation of the situation. Generally speaking, a precancerous lesion deserves treatment, although a diffuse precancerous process may be kept under observation until cancerous change seems imminent. Again speaking generally, the entire precancerous tissue should be removed, not just a single lesion or a small region.

For destruction or removal of one or several lesions one can choose from the following types of treatment: chemical; thermal, usually heat, occasionally cold; electric currents of high frequency; excision by scalpel or occasionally by curet; irradiation by x-rays or radium.

Excepting the controlled chemotherapeutic method of Mohs, there is little use for application of acids, etc. Only the earliest stage of an as yet shallow or ill-defined keratosis will respond well to painting with trichloroacetic acid, for example, and particularly well after shallow curettage. More often a keratosis at any stage of development can best be destroyed by electrosurgery. If a malignant change seems already to have occurred, it may be better to excise the entire lesion. If biopsy has been performed and malignancy demonstrated somewhat unexpectedly, then one may prefer radiotherapy to the remaining tissue or to the previously treated base if an inadequate technic may have been used. Unless there is specific indication for it, excision is to be avoided because it usually leads to greater expense and inconvenience for the patient and physician. Electrosurgery in capable hands offers a number of advantages in lesions of the size most often seen today; it is timesaving, convenient, inexpensive, in terms of personnel, equipment and space, and it gives a good cosmetic result, all in addition to an excellent rate of cure.

The management of cutaneous horns and the warty precanceroses is similar to that of senile keratoses.

Nonverrucous epithelial nevi often tend to such multiplicity as to make their prophylactic removal impractical. Early changes of a malignant nature serve as adequate warning of the need for only slightly more extensive removal than when the lesion is in the precancerous stage. This is true because such lesions are basal-cell in nature and slow in growth.

The verrucous epithelial nevi may develop into either basal- or squamous-cell epitheliomas and should therefore be excised prophylactically if small. If they are too large for simple excision to give a good cosmetic result, one may wish to delay, resorting to excision only if and when inflammation, fissure, etc., appear.

Pigmented epithelial nevi can be removed easily by electrosurgery, with or without previous curettage. Excision is indicated if the lesion is large, perhaps 2 cm. or more in diameter. When seborrheic keratoses are numerous, they may as well be left untreated; the likelihood of malignant change is extremely slight in this type of keratosis, as contrasted with

the senile keratosis, but their removal for cosmetic reasons is completely justifiable.

Cysts, too, rarely undergo a malignant transformation and need not be removed until suspicion is aroused by some change in their appearance.

Small areas of Bowenoid change can be destroyed electrosurgically, as can Pagetoid changes, but not Paget's disease of the nipple, which is cancer of the breast; larger lesions may better be excised. Since these lesions are probably an early stage rather than a precursor of cutaneous cancer, one might suspect a need for more radical therapy, but this is not the case because they are so superficial and so slow in growth. It is only after years that they present even early signs of having an invasive tendency. Penile erythroplasia presents a challenge; possibly, there are two types, not distinguishable clinically or even histologically in the early stage in some instances: one precancerous and the other completely benign (a plasmoma). At our present stage of knowledge, the treatment of this condition must be individualized.

Superficial, so-called multicentric, basal-cell epitheliomatosis is a challenge only because the lesions are often both multiple and large when their true nature is recognized. Excision is then suitable. Recently, because of their relatively benign and superficial nature, they have been removed by simple curettage or by dermabrasion with high-speed rotating wire brushes; results seem very satisfactory, as regards both cure and cosmetic result. Small lesions can be successfully treated by electrosurgery.

Summary

In general, then, some precancerous conditions can be left temporarily untreated in aged or seriously ill persons. Precanceroses which characteristically progress only very slowly may be left untreated but should be observed periodically if they are diffuse and extensive or if they are discrete but numerous. The vast majority of discrete precancerous lesions should be destroyed or otherwise removed; usually the technic can be simple and conservative. When there is any, even slight, clinical or histologic indication of progression to malignant transformation, the lesion should be treated in the same manner as if it were already definitely malignant.

Leukoplakia of the Intraoral Cavity

WILLIAM S. MacCOMB*

The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston

WILLIAM S. MAC COMB

LEUKOPLAKIA, meaning "white plaque," is a lesion arising on mucous membranes of the external orifices of the human body. In the oral cavity, leukoplakia has long been recognized as a precancerous condition. Many names have been suggested for this abnormality of oral mucous membranes: leukoplakia, nicotina, hyperkeratosis, leukokeratosis, and many others. Butlin,[1] in 1885, referring to a case report by Sir James Paget of a smoker's patch on the tongue, suggested the term "leukoma." The term "leukoplakia" was first suggested by Schwinner of Budapest, in 1877, and has now come to be universally accepted.[2]

Leukoplakia has been defined by Prinz and Greenbaum[3] as "an intensely chronic inflammation of the mucous membrane of the tongue, cheeks, lips and, less frequently, of the palate, which is characterized by a gradual development of irregular, circumscribed, hard, milk-white, dry patches of keratinized epithelium with an ultimate tendency to malignancy." Leukoplakia of the vocal cords is also frequently seen.

The statement of some authors that the cause can be positively established in the great majority of cases has not been universally accepted. The association of leukoplakia with lues was for many years generally conceded. Now it is evident that in leukoplakia changes first occur in surface epithelium, but in syphilis the reverse is true. Geschickter,[4] in 1933, and Wolbach,[5] in 1937 and 1938, by injecting monkeys with estrogenic hormones, demonstrated the development of hyperkeratinization in the surface layer of the oral mucosa and in epithelial pearls which form in the stratum spongiosum. Later hyperplasia developed in the stratum spongiosum with an inflammatory reaction of the subepithelial corium, which is the histologic picture of hyperkeratosis.

*Chief of Head and Neck Service, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

Nathanson and Weisberger,[6] in 1939, reported that "hyperkeratosis therefore may be considered to be a disease occurring from local irritation in patients who have an inherent tendency to it. This tendency may be inherited, but there is considerable evidence that it may be acquired by general somatic disturbances, such as endocrine dysfunction, avitaminosis and other metabolic conditions."

Hypercholesteremia, suggested by Ullmann,[7] in 1936, as an important predisposing factor to the development of leukoplakia, has not been proved to be a contributing factor in its production. Avitaminosis undoubtedly plays some part in the development of leukoplakia, particularly a deficiency of vitamin A. Mulay and Urbach,[8] in 1958, reported that vitamin A has a marked antikeratinizing effect in both lower animals and human beings, even to some extent when applied locally. Some 30 years ago, constipation was suggested as the cause of oral leukoplakia. Treatment was carried out by daily regulated doses of saturated solution of magnesium sulfate. Many patients were, no doubt, cured of their constipation, with marked improvement in general health, but the leukoplakia usually persisted unchanged.

Smoking in any form has for many years been considered by most authors to be the cause of the development of leukoplakia. Actually, since white patches are found in the oral cavity of nonsmokers, smoking should be considered a secondary aggravating factor but not the primary inciting cause. Bloodgood[9] stated some years ago that tobacco in any form may be the cause or the determining factor but it is the excess, not the form of tobacco used which is the actual causal agent. Many authors have pointed out that not the tobacco itself, but by-products of its combustion or the curing mordants and flavoring compounds used in its preparation, which vary with the finished product, are the true causal factors of the production of leukoplakia. In general, these substances are various salts, sulfates and chlorides, alcoholic extracts of certain aromatic substances, and gums. Many act as vasoconstrictors. As stated by Prinz and Greenbaum,[3] new products are formed during the act of smoking from the combustion of the tobacco and of the substances previously mentioned. Analysis has shown that the end products of combustion are made up of various compounds, all of them highly irritating to the mucous membranes. The heat, the ammonia compound, the phenol-like bodies, and the tarry and oily products seem to be the chief offenders, while the effect of the nicotine is of less importance. It is of interest that the last 2 cm. of cigarettes retain most of the tar and other products of incomplete combustion. The water pipe of the Orient is said to be the least dangerous since the water cools the smoke and absorbs many of the chemical products. In heavy smokers, dryness of the mouth is evident and may be due to decrease in the amount of normal saliva. The effect is first evident as thickening of the mucous membrane, the result of a defense mechanism of the human body. Leukoplakia certainly is found also in the nonsmoker; therefore other contributing factors, perhaps still unknown, may be the true cause.

Thoma[10] has pointed out that the blond, red-haired individual with sun-sensitive skin is prone to production of leukoplakia. This observation has not been confirmed by other writers. In the southwestern United States many of the early settlers were of Scotch, Irish or North European ancestry. Many of their descendants with the characteristic blond complexion are still there. Exposure to the sun produces many skin cancers, but the development of leukoplakia of the intraoral cavity in these people has not been observed, except when associated with the use of tobacco, either in the form of smoking or snuff. The use of tobacco would seem to be a far more important contributing factor to the development of leukoplakia than is the individual's complexion.

Poor oral hygiene and decayed teeth may contribute to the formation of leukoplakia, but actually leukoplakia in such conditions, without the associated prolonged use of tobacco, in our experience, does not occur. The presence of decayed teeth, or the absence of teeth, certainly leads to poor digestion. Poor dental hygiene is often seen in remote rural areas, and unbalanced diets seem to be common among these people. Consequently, avitamino-

sis may well be a contributing factor in the development of leukoplakia.

The use of alcohol also has been suggested as a cause of intraoral leukoplakia and, indeed, of oral cancer itself. The high incidence of excessive use of alcohol in those patients afflicted with intraoral cancer has often been noted. Actually, I have never seen an alcoholic who has not also been a heavy smoker. This statement applies to women as well as to men. The alcoholic person also is subject to a poorly balanced diet, particularly deficient in meat. Therefore, it is hard to disassociate avitaminosis, alcoholism and excessive use of tobacco as causal factors in the development of leukoplakia.

Leukoplakia is more frequently seen in men than in women, but in rural areas in the southwestern section of the United States snuff is widely used, mostly by women. These patients state that they began "dipping snuff" in early childhood. Hence, 40 to 50 years or more have passed with daily application of the snuff to mucous membranes of the mouth. Usually the buccal mucosa, gum or gingivobuccal gutter is the area affected. At the time of her first examination, one patient with cancer of the buccal mucosa, when asked how long she had been using snuff, replied, "over 90 years." Her statement was true. She began at the age of six and was then 96 years of age. Incidentally, patients, when asked to point out the usual site of the placement of the twig or brush bearing the snuff, invariably point to the side opposite the location of the cancer. Inquiry of members of the family, however, usually discloses the fact that the cancer has arisen on an area of mucous membrane habitually contacted by the snuff. Leukoplakia is rarely seen in the Negro except in association with excessive use of tobacco in the form of either chewing tobacco or snuff.

Leukoplakia of the intraoral cavity may be classified clinically as being of three types. The initial reaction of mucous membranes to irritation is hyperemia, followed by blanching of the mucosa, and hyperplasia, an overgrowth of the prickle-cell layer. The flat, nonulcerated, smooth, tessellated plaque of leukoplakia which gives no symptoms is the simplest type of true leukoplakia found (figure 1). Such areas are usually discovered by the patient's dentist. This type of leukoplakia may be the precursor of the more advanced form. Figure 2 shows the microscopic picture of early leukoplakia. The basal cells which normally form an orderly row of parallel cylinders here show slight disruption of this pattern. A thin parakeratotic layer forms at the surface.

The second type is elevated, thickened and fissured, but not ulcerated. The patient who has such a lesion may be conscious of an ill-defined dryness but usually remains asymptomatic until the abnormality is discovered by the dentist or physician. Figure 3 shows a tongue with leukoplakia of this phase. Figure 4 presents the microscopic picture of this intermediate phase of leukoplakia. The epithelium is thickened and the basal cell layer is replaced by several layers of small round cells lying on a sharply undulating or even serrated basement membrane.

The third, or advanced, type is the raised, ulcerated, verrucous papillary growth which borders on squamous cancer and is certainly the precursor of the true cancer. Figure 5 shows this phase of development of leukoplakia occurring in a woman 64 years of age who gave a history of having "dipped snuff" for nearly 50 years. Leukoplakia was most evident on the undersurface of the tongue and floor of the mouth. No active treatment was given. Observation was carried out from 1949 to 1954 when surgical excision was done. It is of interest that this patient presented leukoplakia of the vulva also. Microscopic findings on tissues removed at that time are shown in figure 6.

Figure 7 illustrates the intermediate and advanced stages of leukoplakia. This patient was referred to the hospital because of hoarseness. Leukoplakia was present on the vocal cords and in the intraoral cavity, as shown in the photograph. The patient had been smoking four packages of cigarettes daily for years. Also, he had been drinking more than a bottle of whiskey daily for the past year. No active cancer was found either in the larynx or in the intraoral cavity. He has now discontinued the use of both tobacco and alcohol. The leuko-

FIGURE 1. Leukoplakia in early phase.

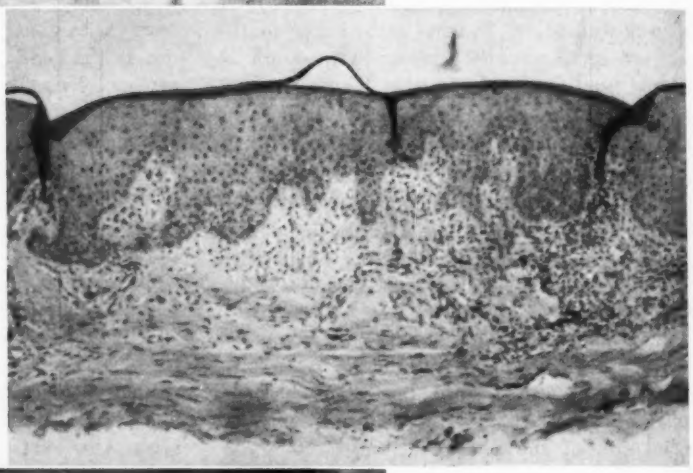


FIGURE 2. Photomicrograph of leukoplakia in early phase.

FIGURE 3. Leukoplakia in intermediate phase.

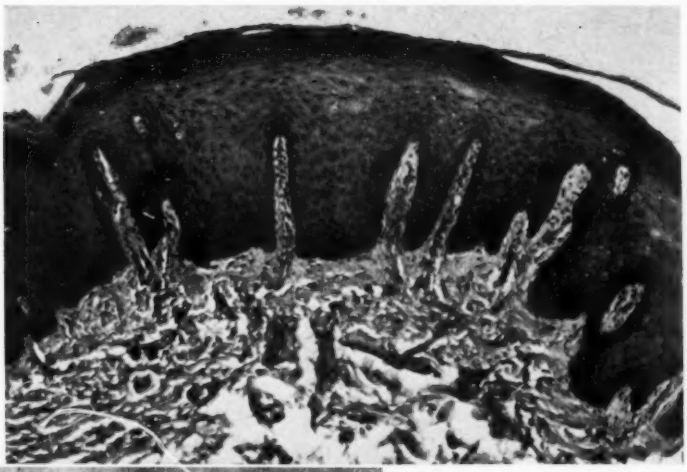


FIGURE 4. Photomicrograph of leukoplakia in intermediate phase.

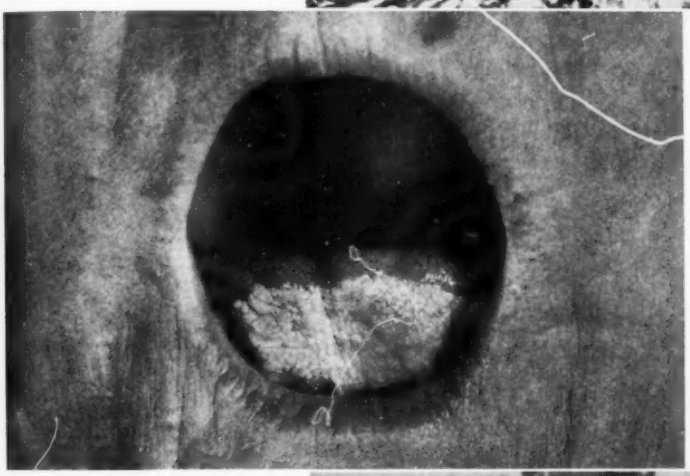


FIGURE 5. Leukoplakia in advanced phase.

FIGURE 6. Photomicrograph of leukoplakia in advanced phase.

FIGURE 7. Mixed type of leukoplakia.

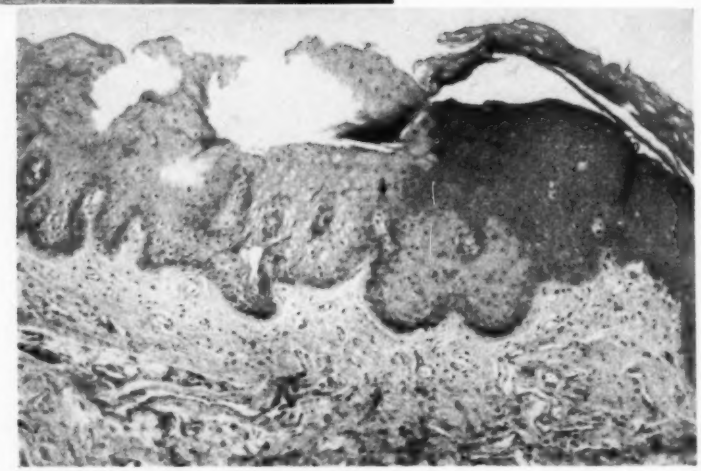


FIGURE 8. Photomicrograph of mixed type of leukoplakia.

plakia of the larynx has nearly disappeared. The leukoplakia of the tongue has been excised and the patient is being kept under close observation.

Figure 8 shows the microscopic findings. The epithelium proliferates both superficially and into the submucosa, leaving slender, well-vascularized folds of connective tissue between the epithelial masses. Scattered epithelial cells with abnormal nuclear chromatin may be present. In all stages of leukoplakia the submucosa contains a variable lymphocytic infiltrate, evidence of local inflammation.

Leukoplakia is a known precancerous lesion; therefore, it should be treated as such. Removal of causal factors is the first step in treatment. Improvement in oral hygiene, treatment of dental sepsis, removal of contributing factors such as tobacco and alcohol, maintenance of a well-balanced diet, and elimination of constipation are all to be considered before the actual treatment of leukoplakia can be instituted.

Some early lesions may be treated with superficial desiccation by electrocautery, either bipolar current or actual cautery. At least they should be kept under close observation. A biopsy, particularly of the second and third types of leukoplakia, is important and must be adequate. All too often adequate treatment

for a fully developed cancer has been delayed until it is too late for cure because the first biopsy was reported to show leukoplakia only. The pathologist making this report was not at fault. The physician taking the biopsy obviously had excised a specimen too small or too superficial for correct diagnosis. Therefore, if the report received from the pathologist is not in accord with the clinical impression, the biopsy should be repeated. Complete surgical excision had best be done, if necessary. Treatment of more advanced areas is surgical, consisting of surgical excision, with primary closure for the smaller lesion and repair by means of a split-thickness skin graft for the larger areas. The presence of a true cancer may not be suspected until microscopic examination is carried out; therefore, all specimens of tissue removed should be examined microscopically. All types of leukoplakia described may occur simultaneously in the same lesion. A biopsy may show only one type. Therefore, a wide surgical excision is to be preferred to a biopsy. Radiation therapy in any form is contraindicated. Leukoplakia is not susceptible to radiation in any form. In fact, leukoplakia may continue to grow in an irradiated field.

The possibility, if not indeed the likelihood, of leukoplakia developing into cancer later is so great that the importance of close observation is evident. Leukoplakia may arise in areas contiguous with those previously treated and may occur following apparently complete excisions. Even under close observation cancer may develop in well-established areas of leukoplakia. Plaques of leukoplakia are known to have existed for years without apparent change. Suddenly the tissues begin to show change and growth, and a fully developed cancer becomes evident. Rather than repeated biopsies of suspected areas of leukoplakia, wide surgical removal of areas in question should be the treatment of choice. Multiple areas of leukoplakia are not unusual, occurring either simultaneously or successively in widely separated areas within the oral cavity. In people who are "snuff dippers," multiplicity of lesions of intraoral cancer is quite common.

Conclusion

That leukoplakia of the oral mucous membrane is a precancerous lesion is well established. Etiologic factors, particularly the association of leukoplakia with the use of tobacco, have been discussed. A simple classification, with representative clinical and microscopic illustrations, has been presented. Treatment of patients with leukoplakia in the early cases may be cauterization if biopsy is negative. More advanced stages should be treated by surgical excision. Close observation is indicated in all instances. As stated by Hertz,[11] the precancerous condition is reversible, but the cancerous is not. Therefore, a well-planned and concerted attack should be made on the cause of leukoplakia.

REFERENCES

1. Butlin, H. T.: Diseases of the Tongue. London, Cassell & Co., 1900. Cited by Prinz and Greenbaum.[3]
2. Cooke, B. E. D.: Leukoplakia buccalis and oral epithelial naevi; a clinical and histological study. Brit. J. Dermat. 68:151-174 (May) 1956.
3. Prinz, H. and Greenbaum, G. G.: Diseases of the Mouth and Their Treatment. Ed. 2, rev. Philadelphia, Lea & Febiger, 1939, p. 246.
4. Geschickter, C. F.: Recent progress in treatment of cancer. Clin. Med. & Surg. 40:73, 1933.
5. Wolbach, S. B.: The pathologic changes resulting from vitamin deficiency. J.A.M.A. 108:7-13 (January 2) 1937.
6. Nathanson, I. T. and Weisberger, D. B.: The treatment of leukoplakia buccalis and related lesions with estrogenic hormone. New England J. Med. 221:556-560 (October 12) 1939.
7. Ullmann, K.: Über seltene und neue Formen der Leukoplakia mucosae oris. Wien. klin. Wchnschr. 45:840-844 (July 1) 1932.
8. Mulay, D. N. and Urbach, F.: Local therapy of oral leukoplakia with vitamin A. A.M.A. Arch. Dermat. 78:637-638 (November) 1958.
9. Bloodgood, J. C.: Cancer of the tongue a preventable disease. J.A.M.A. 77:1381-1387 (October 29) 1921.
10. Thoma, K. H.: Oral Pathology. Ed. 4. St. Louis, The C. V. Mosby Company, 1954, p. 964.
11. Hertz, J.: Oral precancerous lesions with special reference to role played by dentist in cancer prevention. Oral Surg. 9:687-698 (July) 1956.

Precancerous Lesions of the Uterus; How to Treat Them

JOHN B. GRAHAM*

Roswell Park Memorial Institute, Buffalo

ADENOMATOUS hyperplasia of the endometrium and carcinoma *in situ* are the two precancerous lesions of the uterus that we recognize. Either may accompany invasive cancer. Surgical excision offers the simplest and most satisfactory form of treatment.

JOHN B. GRAHAM

Adenomatous hyperplasia of the endometrium is to be distinguished from simple cystic dilatations which are of little consequence and very common after the menopause. Adenomatous hyperplasia is found in association with endometrial cancer in 16 to 40 per cent of cases.[1-3] The frequency with which cancer subsequently develops in women with hyperplasia is uncertain, but it occurs in perhaps 1 to 5 per cent of cases.[4]

Carcinoma *in situ* of the cervix is frequently found at the margin of an invasive cancer—in 60 to 75 per cent of cases.[5] Roughly in 10 per cent of patients with carcinoma *in situ* alone true cancer has developed subsequently if the lesion was untreated.[6]

About two-thirds of cases of endometrial hyperplasia attract attention because of abnormal bleeding; i.e., menorrhagia, metrorrhagia or postmenopausal bleeding. There are no symptoms of carcinoma *in situ* of the cervix, although the patient may have bleeding or discharge from some coincident lesion.

Exfoliative cytology is a potent force in detecting these lesions. In our laboratory, 96 per cent of positive vaginal smears for adenocarcinoma came from a demonstrable cancer, mostly of the uterine body. The remainder came from hyperplasia. Eighty-two per cent of vaginal smears reported positive for squamous carcinoma are found in patients with cervical cancer. Fifteen per cent arise from carcinoma *in situ* and the remaining 3 per cent come from atypical epithelium.

What should be done with the patient who has endometrial hyperplasia, carcinoma *in situ* of the cervix, or a positive smear and no apparent cancer? Our program is as follows:

The patient is admitted to the hospital and given a thorough general examination, because multiple cancers are more common than generally realized. (In our series of more than

*Chief, Department of Gynecology, Roswell Park Memorial Institute, Buffalo, New York.

4000 patients with cancer of the cervix who were followed 7 to 40 years, a second cancer developed in 20 per cent of those who did not die of the cervical cancer.)

The patient is examined under anesthesia to detect the presence of invasive cancer and to determine the extent of the premalignant lesion. In order to reduce the nursing load, we do not shave the perineum. PENTOTHAL® sodium is used. After bimanual palpation, the cervix is inspected in a good light. Carcinoma *in situ* is sometimes visible as a red, slightly raised, velvety area. Schiller's iodine solution may indicate an unstained area for biopsy on an otherwise unremarkable cervix. A small curet, such as Duncan's, should be used to systematically explore the walls of the endocervix. The examiner should feel for areas of cancer which are softer and more easily scraped off or penetrated than the normal tough endocervix.

If the cervix is suspect, the cervical biopsy is done next; if the endometrium is in question, the curettage is done first. I prefer to do the curettage first if there is no indication. Diagnostic curettage is different from the obstetric treatment of retained products of conception. Each stroke in the diagnostic procedure should begin in the distant fundus and be carried down and out of the external os so as to yield a strip of endometrium. The familiar churning technic is condemned. It gives bits and pieces that limit analysis. The curettage should systematically cover the entire cavity. After the diagnostic procedure is completed, if hyperplasia is found and there is doubt concerning removal of all the redundant epithelium, the surface may be covered again with short strokes in order to complete the job.

The cervical biopsy is simplified if there is a visible lesion, for a wedge can be taken that includes the abnormal tissue as well as the adjacent normal epithelium. A similar procedure is used on Schiller-positive and Schiller-negative areas. A sharp knife yields the best results, care being taken not to handle the specimen with a forceps which pinches and distorts it. Diathermic biopsy is not used because the cooked cells cannot be evaluated. A punch biopsy is easier to do and yields a satisfactory specimen if the instrument is sharp. I prefer a Younge cervical forceps or a Stille nasal septum forceps. Both are expensive—about $70. They must be cold sterilized to preserve the edge. Hemostasis is obtained with a catgut suture or local pressure with a silver nitrate-tipped stick.

If there is no visible lesion but the patient has a positive smear or record of previous positive biopsy, four-quadrant small biopsies plus the endocervical cureting mentioned or a cold-knife cone biopsy should be done. My preference is the former procedure because healing is more prompt and kindly. I have never had difficulty using quadrant biopsies that I thought would have been avoided by doing a cone biopsy. However, we do use cone biopsies in our clinic. They are of particular value in the young woman in whom the childbearing function is desired. After a cone biopsy, hysterectomy must be delayed for at least a month in order to avoid complications.

If histologic section of the obtained material fails to show cancer, the physician is left with the problem of what to do with the premalignant lesion.

Patients with endometrial hyperplasia can be followed. If they bleed again or continue to have positive smears, a repeat curettage is indicated. If more bleeding occurs or the positive smear persists, a total hysterectomy is indicated. Our rule is "two curettages and out."

An example of this problem is our patient No. 90790, age 65, a diabetic in cardiac failure, with vaginal bleeding, and a positive smear. Four curettages in one year showed only adenomatous hyperplasia. A hysterectomy at 14 months showed a small adenocarcinoma in one cornu. She is living and well two years later.

Patients with carcinoma *in situ* of the cervix are best treated by total hysterectomy with a vaginal cuff of 1 cm. or more. A preliminary Schiller test helps to outline the lesion. If the lesion runs out on the vagina, the margin of dissection, a good centimeter beyond, should be marked by incising the vagina. Preservation of the ovaries is important in the premenopausal woman. Patients who are eager to have children should be given the opportunity

to do so if they will be seen regularly. These women can be followed at two to three month intervals by examination and vaginal smear. If they have further symptoms, such as bleeding, or if the malignant cells in the smears undergo progressive loss of differentiation, repeat examination under anesthesia and biopsy are indicated.

We have a series of 15 patients with carcinoma *in situ* who were followed without treatment for periods of four to seven years. Three patients showed progression but none developed frank invasive cancer. Five regressed completely. One patient went through two pregnancies, and when she had a hysterectomy four years later (because I moved and could no longer follow her), carcinoma *in situ* was still present. An alternate method is to remove the carcinoma *in situ* by conization and then follow the patient. This is a reasonable procedure, but one with which I have had no experience.

Precancerous lesions of the uterus are poorly defined, because not many patients have been carefully examined and then followed without treatment.

Summary

From what we know, adenomatous hyperplasia of the endometrium and carcinoma *in situ* are precancerous lesions. They are even more likely to be found in association with invasive cancer. Therefore, patients with these lesions must be studied carefully to detect the presence of cancer. In the absence of demonstrable cancer, curettage may suffice for the hyperplastic endometrium. However, if symptoms persist, hysterectomy is indicated. Carcinoma *in situ* of the cervix is treated by total hysterectomy with an adequate margin of vaginal cuff.

REFERENCES

1. Copenhaver, E. H.: Atypical endometrial hyperplasia. Obst. & Gynec. 13:264-268 (May) 1959.
2. Gusberg, S. B., Moore, D. B. and Martin, F.: Precursors of corpus cancer. A clinical and pathological study of adenomatous hyperplasia. Am. J. Obst. & Gynec. 68:1472-1481 (December) 1954.
3. Novak, E. and Yui, E.: Relation of endometrial hyperplasia to adenocarcinoma of the uterus. Am. J. Obst. & Gynec. 32:674-698 (October) 1936.
4. Greene, R. R., Roddick, J. W., Jr. and Milligan, M.: Estrogens, endometrial hyperplasia and endometrial carcinoma. Ann. New York Acad. Sc. 75: 586-600 (January 9) 1959.
5. McKay, D. G.: Personal communication to the author.
6. Erickson, C. C., Everett, B. E., Jr., Graves, L. M., Kaiser, R. F., Malmgren, R. A., Rube, I., Schreier, P. C., Cutler, S. J. and Sprunt, D. H.: Population screening for uterine cancer by vaginal cytology; preliminary summary of results of first examination of 108,000 women and second testing of 33,000 women. J.A.M.A. 162:167-173 (September 15) 1956.

Precancerous Lesions of the Stomach; How to Treat Them

RUSSELL S. BOLES*

University of Pennsylvania School of Medicine, Philadelphia

RUSSELL S. BOLES

THE purpose of this paper is simply to present an opinion which, I am sure, is shared by many concerning so-called precancerous lesions of the stomach.

In view of an apparent change of incidence of cancer of the stomach,[1] which does not parallel the varying figures on the incidence of generally accepted precancerous lesions, it seems appropriate to re-examine the controversial relationship of these lesions to cancer.

First, however, it is necessary to define just what is meant by a precancerous lesion. In searching the literature one is dismayed at being unable to find a definition that really tells us anything at all. Pathologists and surgeons venture no opinion except to say that they recognize certain benign lesions that will, if given time, become malignant. Herbut[2] said, "The term is valid if used discreetly, although it is not acceptable by all workers in the field." No one has the slightest idea how long a time will be required for the transformation to cancer, whether months or years, but the idea is given that if the patient lives long enough cancer will develop. The term precancerous then, to say the least, is highly ambiguous. Furthermore, there is no unanimity of opinion concerning its application to conditions involving the stomach.

"Precursor" is another expression loosely used synonymously with precancerous. The only thing in favor of the word precursor is that it does not carry the foreboding implications of the word precancerous. Neither of these terms should be confused with carcinoma *in situ*. Boyd[3] has defined carcinoma *in situ* as an area of epithelium that has developed the cytologic changes of malignancy without invasion of the underlying connective tissue. The cytologic changes, while helpful, are not always specific of cancer but may be mimicked

*Professor Emeritus of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, and Special Consultant, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

by other processes, such as inflammation. In a certain number of cases, carcinoma *in situ* is said to become invasive; it is also thought at times to be reversible. Reimann[4] expressed the opinion that invasion on the part of cancer cells into the surrounding tissue is the best single microscopic criterion of malignancy. How long it takes for transition from the *in situ* state to the invasive state is not known, but it must be influenced by many variables.

That there should be much confusion concerning these questions is to be expected when pathologists of experience do not agree on absolute histologic criteria for the precancerous state or for the diagnosis of carcinoma *in situ*. As my main theme in this paper concerns the interest of all patients rather than a selected few, I would emphasize at this point the caution expressed by Reimann relative to the diagnosis of precancerous states and carcinoma *in situ;* i.e., "Obviously both diagnoses and their implications involve a prophesy, and prophesy of details in biology is hazardous."

The specific conditions affecting the stomach which are held to be precancerous are peptic ulcer, polyps, chronic atrophic gastritis and pernicious anemia. Unfortunately, there is no incontrovertible proof that transition from a benign to a malignant state ever actually occurs in any of these affections. An important reason for this is our inability to examine the suspicious tissue under the microscope and in the patient at one and the same time. Lacking such proof, there is naturally a great deal of uncertainty concerning such transition and, as a result, one is forced to the conclusion that such changes in diagnosis are based more on presumption than fact. Although the etiology of the conditions mentioned is as unrevealed as that of cancer itself, I am aware that some will claim that it would be folly indeed to say that none of them ever becomes cancerous. On the other hand, I believe, in the light of our present inadequate knowledge, that radical treatment based on widely varying statistical data is folly compounded.

Gastric Ulcer and Cancer

The controversy about the peptic ulcer-cancer problem has been going on for many years and is still far from solution. Will it ever be solved unless some extraordinary new instrument for diagnosis is invented? Some pathologists claim that cancer may develop in the margin of a pre-existing chronic peptic ulcer; on the other hand, typical peptic ulcers have been found within a cancer. What we need to know is how frequently a benign ulcer becomes malignant. As far as I can see, it is impossible to say. There are those who claim that this never happens, while others venture an opinion that it happens in 10 per cent, or more, of the cases; at one time it was estimated at 70 per cent and higher! All of the latter opinions are based on operative or autopsy material, disregarding entirely the vast number of ulcers that never come to the operating table or to necropsy. We must never forget that there can be a vast difference between the number of reported cases of a disease and that of cases actually existing. And who can prove, even after operation, that an ulcer with a malignant margin, as shown histologically, had ever been a benign lesion or that it was a malignant lesion undergoing peptic ulceration? It is said that either transformation may occur. No longer does the location or size of an ulcer assist in the diagnosis, although at one time both of these characteristics were regarded as important; the diameter of 2.5 cm. used to be the dividing line.

The fact that most cancers and peptic ulcers originate in the lower third of the stomach, the cancers being nearer the pyloric canal, does not justify any correlation between the two lesions so long as there are unknown variables affecting each of them which must be taken into account. Correlation can erroneously be arrived at through an extrapolation of statistics, which means, of course, that something will happen to a certain number as judged by their previous occurrence. Among variables to be reckoned with are age, sex, race, heredity, environment, geographical location, diet, alcohol, tobacco and numerous other agents of possible carcinogenic nature.

The differential diagnosis of a benign gastric ulcer supposedly undergoing carcinomatous change and an early malignant ulcer of the stomach is fraught with many difficulties.

The problem might be simpler if benign ulcer of the stomach exhibited the rather typical symptomatology of the uncomplicated duodenal ulcer. That their symptomatology is so often dissimilar may be due to the probability that their pathogenesis is different, although they do present a similar histologic picture. Certainly, as far as cancer is concerned, malignant transformation of benign duodenal ulcer is unheard of, and primary cancer of the duodenum is an exceedingly uncommon lesion.

The decision as to whether or not an ulcer of the stomach is malignant, regardless of its primary nature, is of paramount importance from the standpoint of its management. If malignant change in a benign ulcer is suspected, then proof that a benign ulcer had existed at the site should be conclusive. Usually this is not the case. The duration of symptoms, short or long, and the demonstration of an ulcer that presumably had healed on one or more occasions cannot be accepted as proof. Admittedly, however, such behavior is strongly suspect. The history, which should provide the cornerstone in diagnosis, unfortunately, will not be as helpful in detecting an incipient lesion as it might be in the case of a well-established lesion. X-ray examination continues to hold undisputed priority over other objective methods in making a diagnosis. Its accuracy has been held to be as high as 90 per cent. Templeton[5] strikes a very optimistic note regarding roentgenologic diagnosis by stating, "No longer need the doctor guess when the question is asked 'Is the gastric ulcer benign or malignant?' " He bases his opinion on the results obtained by Kirsh in the radiologic examination of gastric ulcer combined with other methods of examination, especially endoscopy and cytology. Kirsh,[6] in a review of 100 cases of proved carcinoma of the stomach, showed that an accurate preoperative x-ray diagnosis was made in 81 per cent. In the 100 cases, only one case of carcinoma was considered to be benign gastric ulcer on preoperative x-ray examination. Kirsh's criteria were based on the mucosal relief and compression technics.

In the differentiation of benign and malignant lesions of the stomach, cytologic studies are becoming of increasing assistance. However, the rigid technical requirements and the need for highly experienced personnel and for pathologists especially qualified in this field preclude its usefulness except in clinics particularly equipped for such studies.

Gastroscopic examination is of assistance in supporting the roentgenologic findings and, in addition, may indicate the nature of the lesion as well as the limits of operability.

If the evidence secured from the examinations mentioned affords a reasonable suspicion of malignancy, there can be no question that without further ado, operation should be advised. By the time suggestive symptoms, such as loss of appetite, loss of weight and energy, anemia, etc., occur, the diagnosis has, no doubt, become obvious, and favorable prospects from surgery have greatly diminished. A little later I shall allude to the matter of surgery for all uncomplicated gastric ulcers.

Polyps and Cancer

Polyps, single or multiple (diffuse polyposis), are other so-called precancerous lesions of the stomach still subject to much controversy. The statistics here on incidence and management, as in the case of ulcer, vary widely, a good deal of the variation depending on whether the observations were made on surgical or autopsy material. The incidence may be affected by the fact that protrusions of mucosa in hypertrophic gastritis are mistaken at times for true polyps. Polyps occur in general in the same locations as cancer of the stomach and, as in the case of cancer, are associated with chronic gastritis and low or absent acid secretion. Acid values in early cancer, however, are found at times to be within normal limits. It has been thought that the incidence of polyps increases with the duration of achlorhydria. Gastric polyps appear in about the same ratio as does cancer in respect to sex and age.

The cause of polyps is unknown and pathologists are not in agreement concerning their exact histopathologic nature. One must wonder whether heredity plays a part in the development of polyps of the stomach as it surely does in polyposis of the colon. As a re-

sult there is confusion in classification which prevents an accurate estimation of incidence of types. The term "polyp" itself signifies nothing more than a gross physical characteristic which, of course, is entirely inadequate. However, it has been in use so long that any attempt to change it would only lead to further confusion in diagnosis.

The diagnosis of uncomplicated gastric polyp will usually be made by accident during the search for some other disease such as peptic ulcer, cancer or cholecystitis. When symptoms occur in the presence of a polyp, they are probably due to associated atrophic gastritis or to some extragastric disease. Should a polyp impinge on either orifice of the stomach, disturbances of motor or secretory function due to intermittent pyloric obstruction and intussusception may occur. Other complications may be gross or occult bleeding with the development of anemia. Incidentally, in any case of obscure anemia, careful investigation of the digestive tract is advisable, bearing in mind, particularly, the possibility of polyps, ulcer and carcinoma.

Our primary concern in this matter deals with the question of malignancy. As polyps are usually associated with hypoacidity or achlorhydria, regardless of malignancy, the acid findings are of no help in determining whether malignant transformation has taken place, nor will this be determined by x-ray examination, although the polyp itself is easily revealed. Gastroscopic examination may be of assistance if a biopsy specimen with surrounding tissue can be secured from a suspicious area of the polyp to determine whether invasion has occurred. Final determination of malignancy can only be made by a histologic examination.

As in the case of ulcer, there are those who believe that once the presence of a polyp has been established by x-ray, and perhaps gastroscopic examination, it should be removed. It goes without saying that any polyp which contains carcinoma *in situ* or causes symptoms of obstruction or is associated with gross or occult bleeding, anemia and indigestion of any type should be treated surgically. If one concludes that a polyp is benign, simple excision is all that is necessary. Fortunately, in the great majority of cases it must be conceded that polyps account for very few cancers; those that do are over 2 cm. in diameter. This being the case, surgery can be safely deferred, barring the complications mentioned.

When operation is deferred, whether the polyps are single or multiple, frequent examination of the lesion is advisable as well as a careful check on the patient's history. Such re-evaluation entails periodic x-ray and gastroscopic examinations at least every four to six months. In the absence of symptoms, as is usually the case, the inclination of the patient to evade such examination becomes apparent. Nevertheless, the necessity for checkup examinations should be strongly emphasized. Operation on polyps considered malignant requires resection of the stomach, because cancer has been known to recur at the site of an original growth receiving simple excision. Following resection, periodic examination of the residual gastric pouch must be made because subsequent polyps and cancer in this area have been known to occur.

Gastritis and Cancer

Chronic atrophic gastritis has long been regarded as a precursor of cancer. This assumption would seem logical if, as some believe, stomachs with atrophic gastritis are particularly prone to cancer. It is well recognized, of course, that in practically all cases of carcinoma of the stomach some degree of atrophic gastritis is present. Again, this in no sense implies a cause-and-effect relationship. Atrophy of the glandular parenchyma of the gastric mucosa increases with age, and with it an increasing incidence of achylia and gastric carcinoma also occurs. If there is proof of any consistent sequence or direct relationship between these conditions, one causing the other, it has escaped my attention. If one is apprehensive about atrophic gastritis, especially if it is accompanied by pernicious anemia, then one should recommend checking up by x-ray, gastroscopic examination, and cytologic examination of gastric washings once or twice a year, something that the patient will not accept too kindly. I make the latter qualification

because these patients, in the absence of other disease, are relatively free of symptoms. I am not impressed with any such symptomatology as anorexia, epigastric distress, loss of weight, lassitude, etc., as indicative of chronic atrophic gastritis. In fact, I believe that the diagnosis of such a clinical entity is again one of those things based more on presumption than fact. The atrophic mucosa may be well recognized through the gastroscope, and we know that these people have little or no acid secretion. Despite their age, they can eat like horses, often with little regard to what they eat, and feel fit as a fiddle. As for the chronic alcoholic, how often do we see him suffer from his customary gastritis!

I shall not go into details concerning the treatment of atrophic gastritis. Regeneration of tissue does not occur, as far as we know, because the original cause is still present. Therefore, diet, substitution therapy with vitamins, etc., would seem unnecessary. Theoretically, however, such therapy may be indicated in certain cases. I can remember Sir Arthur Hurst, many years ago in his clinic in Windsor, England, providing each table in the dining room with a pitcher of what looked like pink lemonade—a mixture of dilute hydrochloric acid, lemon juice and a little grenadine, which the patients with achylia gastrica consumed with evident pleasure. A dash of something else, no doubt, would have enhanced the euphoric effect of such therapy!

Pernicious Anemia and Cancer

Pernicious anemia has been suspected of being a precursor of gastric cancer. The only possible excuse for such an assumption is that patients with pernicious anemia have atrophic gastritis and achlorhydria, and cancer of the stomach is said to develop three times more frequently in patients with pernicious anemia than in other patients of comparable age groups. Some say 10 to 20 times! There is not a shred of evidence, however, to prove that one leads to the other. There are, of course, a number of interesting theories concerning the relationship of these conditions which cannot be discussed at this time.

Once the diagnosis of pernicious anemia has been established, it would be reasonable to advise careful examination of the stomach. This would require x-ray and gastroscopic examination and, if dependable facilities are available, cytologic examination of gastric washings. It is interesting that the smooth appearance of the tongue, due to atrophy of the papillae in pernicious anemia, bears a striking resemblance to the atrophy and smooth appearance of the mucous membrane of the stomach in atrophic gastritis. I know of no suggestion, however, that the atrophic condition of the tongue is a precursor of cancer or in any way favors the development of cancer of that organ.

Moral Considerations

It would seem that anyone who has really focused his attention on this subject would realize by now that certain concepts we hold about precancerous lesions of the stomach are outmoded. It is unfortunate enough that they are unscientific and without foundation, but it becomes calamitous in the lives of many patients when they lead to unnecessary and disabling surgery, all of which is performed in good conscience in an attempt to reduce the incidence of cancer of the stomach.

The strong differences of opinion concerning the early diagnosis of gastric cancer and the probability of cure from operation call for a renewed and realistic appraisal of this whole matter. There are moral considerations as well as physical ones involved here that require emphasis. For instance, let us suppose that among 100 patients who were being medically treated for a benign peptic ulcer there were 10 per cent who were proved to have cancer when operated on. This situation raises several vitally important questions which demand a conscientious and forthright answer.

The first of these questions concerns the use of the word "precancerous." There is no agreement as to what constitutes a precancerous lesion of the stomach, nor even a definition of the word that fulfills in the slightest way any criteria that are scientifically acceptable. The word connotes possible impending tragedy in a patient's life. Also, by focusing attention unwarrantedly on a perfectly be-

nign process as a harbinger of death, its use creates unending anxiety on the part of the patient and leads to disabling operations by surgeons of good intent who are consumed with a desire to help the few at the expense of the many. For the reasons mentioned, the word should be abandoned.

The second question concerns the matter of diagnosis. The recognition of an ulcer or a polyp in the stomach usually is not difficult for an experienced radiologist. Whether the ulcer is of a malignant nature or whether the polyp harbors malignancy is quite another matter. I have already cited the role of the history and of various procedures that may be helpful in determining the diagnosis. The fact that all diagnostic methods may fail us at times does not justify untimely surgery. Unfortunate as mistakes in diagnosis may prove to be, they should arouse us more to the urgent necessity of improving our methods of diagnosis rather than encouraging the sacrifice of many stomachs which would have been amenable to medical management. Analogous situations would be the amputation of the breasts of all women with a lump in the breast in order to spare some 20 per cent who are destined to develop cancer of the breast, and the removal of all thyroids containing a nodule because a reported "17 per cent of the nodular thyroids removed contain actual or potential cancer" (note the word "potential").

The third question concerns the management not of precancerous lesions, but of a lesion that is considered malignant after a trial period of observation—it may be one week in one case or six weeks in another. During that period, if the referring physician and the surgeon can agree that there is a reasonable suspicion of malignancy which has been based on appropriate studies by qualified individuals, then, of course, there should be no delay in resorting to surgery.

The final question concerns the matter of research in this field of cancer. What is cancer? Smithers[7] of the Royal Cancer Hospital in London says, "The persistent use of this ill-defined word 'cancer,' as though it represented a specific disease instead of a composite facet of tissue malformation, is misleading and unscientific." He further goes on to say, "Since the term can have no precise boundaries this side of death, it would be better if we were to abandon its use in communications having some pretense to scientific reporting."

Considering the doubts, then, that beset us on all sides concerning the pathogenesis and treatment of this disease complex and the discouraging progress that has been made in its conquest, it is self-evident that research must be directed on a wide, wide scale into new and more promising channels, if the cause of cancer is ever to be found. Certainly, the more we know about the cause of any disease, the more satisfactory its treatment will be. And the cause of cancer in human beings is more certain to be found, in my humble opinion, in the study of human beings. The kind of study I have in mind is well illustrated by the American Cancer Society's Cancer Prevention Study, which outlines a program entailing a detailed investigation of the patient's life at home and at work. This study encompasses the patient's total environment including the effect of emotional disturbances, spiritual influences, and immunologic and many other factors. The potentiality of research of this sort has been stressed by your president, Dr. Pendergrass.[8] How tragic it is that opportunities to carry on such investigations among such groups of people as the Navajo and Piman Indians, to mention only two, are so persistently ignored! To support my point, one may ponder on the survey of the lung and female pelvis of the Navajo Indians, in their reservation in Arizona, which was conducted by Salsbury et al.[9] This study revealed, among other things, an astonishing absence of cancer of the breast. The authors suggested that the lack of trauma from brassières, the universal custom of breast feeding, the diet, and additional factors other than genetic may be responsible. The absence of other types of malignant disease among the Navajos has become apparent, or at least has been suspected, as a result of this survey. As further illustration of the benefits that might accrue to our knowledge of cancer if a similar type of research were pursued, we may cite the work of Hesse,[10] who showed that the Piman Indians of southern Arizona have very little

heart disease, only three cases of myocardial infarction being definitely diagnosed among 2,683 Piman Indians over a two year period.

I am aware, of course, that increasing attention is being given to large-scale epidemiologic and environmental studies of the sort I have mentioned, but I maintain that there are still tremendous opportunities and untapped reservoirs in such areas of study that have too long been incredibly neglected. If an equivalent amount of the money and effort expended on experimental research in the pathogenesis and therapy of cancer were devoted to the study of man in his native environment, the knowledge relevant to cancer which could be secured might well stagger the imagination. Indifference to epidemiologic and environmental research of the type alluded to, I believe, constitutes a true precancerous state of affairs of which our profession and many of those engaged in research should take full cognizance. Such research would engender a more helpful attitude on the part of the public and of many individuals within our profession who are at present resigned to a state of defeatism. It would, furthermore, bring the public closer to an understanding of all the scientific efforts being made to solve the problem of cancer and would put an end to their regarding those efforts as something which is taking place in outer space, far beyond their comprehension. To lend emphasis to my point, I again quote Smithers: "The public view of the pathogenesis of cancer is quite unreal, being governed by fear and hope instead of knowledge and understanding." This being the case, it is the responsibility of the profession to provide the public, in the manner that I have outlined, with more realistic knowledge concerning cancer so that they may enjoy a better understanding of the disease and be privileged to harbor increasing hope and diminishing fear.

REFERENCES

1. Boles, R. S. and Baum, W. S.: An apparent change of incidence in cancer of the stomach. Gastroenterology 28:367-377 (March) 1955.
2. Herbut, P. A.: Pathology. Ed. 2. Philadelphia, Lea & Febiger, 1959.
3. Boyd, W.: Pathology for the Surgeon. Ed. 7. Philadelphia, W. B. Saunders Company, 1955.
4. Reimann, S. P.: Personal communication to the author.
5. Templeton, F. E.: The gastric ulcer—benign or malignant? (Editorial.) Gastroenterology 37:109-110 (July) 1959.
6. Kirsh, I. E.: Roentgen diagnosability of gastric ulcer; a review of 100 proved cases of carcinoma of the stomach. Gastroenterology 37:53-59 (July) 1959.
7. Smithers, D. W.: On the pathogenesis of cancer. Lancet 1:589-593 (March) 1959.
8. Profile: Dr. Eugene P. Pendergrass. Cancer News 13:17 (Winter) 1959.
9. Salsbury, C. G., Howard, F. H., Bassford, P. S., Jr., Atkinson, G. R. and Green, R. W.: A cancer detection survey of carcinoma of the lung and female pelvis among Navajos on the Navajo reservation. Surg. Gynec. & Obst. 108:257-266 (March) 1959.
10. Hesse, F. G.: Incidence of cholecystitis and other diseases among Pima Indians of Southern Arizona. J.A.M.A. 170:1789-1790 (August 8) 1959.

Precancerous Lesions and Other Conditions of the Thyroid Gland

THOMAS J. ANGLEM*

Boston University School of Medicine, Boston

THOMAS J. ANGLEM

THE use of the unqualified term "precancerous lesions" in the title of this paper implies a greater degree of certitude regarding the subject than is perhaps fully justified by our present knowledge. The existence of premalignant lesions which subsequently become cancers is doubted by many, yet there are many others who, since the classic studies of Graham,[1] believe that a large percentage of thyroid cancers have their inception in preexisting adenomas.

Historically, speculation regarding the genesis of human thyroid cancer has centered around the observation of a greatly increased incidence of thyroid cancer in areas of severe endemic goiter resulting from iodine deficiency. Wegelin,[2] in his classic review in 1928, and many others since have emphasized this association.

*Assistant Professor of Surgery, Boston University School of Medicine, Boston, Massachusetts.

The observation that in endemic goiter areas in Switzerland the incidence of cancer was 10 times greater than in the United States as a whole has been repeatedly made. Following correction of iodine deficiency in these areas, thyroid cancer has been reported to have diminished by two-thirds, providing substantial evidence that iodine prophylaxis reduced the incidence of cancer. Similar, but less striking observations have been made with respect to an increased incidence of thyroid cancer in endemic areas in the Great Lakes region of the United States. It is generally agreed that the initiating goitrogenic factor in these areas has been a deficiency of iodine.

In more recent years, extensive experimental work on thyroid disease has yielded data which throw considerable light on the fundamental physiopathology of thyroid disorders in general, and on some of the factors concerned with the development of goiters and of thyroid tumors. A large number of goitrogenic factors, in addition to lack of iodine, have been identified. Some of the more important are thiourea and related compounds, ionizing radiation, and thyroid insufficiency resulting from partial thyroidectomy.

The common denominator in all of the goitrogenic factors, with the possible exception of ionizing radiation, is an interference with thyroid hormone synthesis, storage and release. The reduction in the output of thyroid hormone results in an increase in the secretion of thyrotropic hormone, which produces a hyperplasia of thyroid epithelium and the development of a compensatory enlargement of the gland, or goiter.

The application of these various goitrogenic factors, singly or in combination, yields a series of changes in the thyroid glands of rats and mice which histologically resemble all of the changes observed in the human thyroid, including simple hyperplasia, adenomatous change, adenomas and, under some conditions, metastasizing cancer. These changes develop in the order listed and are reversible to a very considerable extent by feeding desiccated thyroid to the animal, indicating their dependency on thyrotropic hormone. Under some conditions, after prolonged stimulation, these originally dependent tumors become autonomous and no longer require stimulation by thyrotropic hormone to maintain their growth.

These observations in the laboratory, combined with clinical experience, have led to the hypothesis that in human thyroid cancer the initiating factor, a goitrogen, causes impairment of the ability of the gland to secrete thyroid hormone. This, in turn, results in stimulation of secretion of thyrotropic hormone by the anterior pituitary and leads to the development of goiter first, and then, possibly after long-continued stimulation of the thyroid, to cancer. This hypothesis, if valid, provides some support for the belief that the changes observed in the adenomatous gland may be precancerous, or at least provide a soil in which cancer is more likely to develop.

The extent to which the interpretation of these observations on the experimental animal may be carried over to the human is far from settled, but that some human thyroid cancers, principally of the papillary variety, respond favorably to treatment with desiccated thyroid is well established.

Some thyroidologists, on the basis of this hypothesis, have advocated the treatment of nodular goiter with desiccated thyroid. Greer and Astwood[3] have reported a 67 per cent favorable response and disappearance of nodules in 37 per cent. Favorable responses were more likely to occur in recently developed nodules. Crile's[4] experience was much less impressive. He found that only 5 per cent of treated nodules disappeared, although the majority became smaller and none increased in size. Our own experience in a small series of nodular goiters of the type in which surgical treatment would normally be considered was even less impressive. After treatment with 3 gr. of desiccated thyroid for periods ranging from four to six months, none disappeared and none became perceptibly smaller. None increased in size, but it is not at all unusual for nodular goiters of this type to show no appreciable growth within such short periods of time. This discrepancy in results suggests to us that Greer and Astwood are not treating the kind of goiter that would be considered of surgical significance and that nodules of larger size have already attained some degree of autonomy.

Attractive and logical as this hypothesis appears to be on the basis of the observations on experimental animals, there are many inconsistencies in clinical experience with human thyroid cancer which are difficult to reconcile and which suggest that other factors are involved. First of all, there is no conclusive evidence, as yet reported, of the development of thyroid cancer from the ingestion of known goitrogens or from the reduction of the amount of thyroid tissue by partial thyroidectomy. Secondly, as Sloan[5] has reported, 71 per cent of thyroid cancers occur in glands which are otherwise normal and show none of the changes which would be expected from prolonged excessive stimulation by thyrotropic hormone. And finally, a large percentage of thyroid nodules fail to respond to treatment with desiccated thyroid.

The place of ionizing radiation as a goitrogenic or cancerogenic agent deserves special mention. While the production of hypothyroidism by roentgen irradiation or by ingestion of I^{131} may result in increased secretion of thyrotropic hormone, as with hypothy-

roidism produced by other means, it seems probable, by analogy with the effect of ionizing irradiation on other organs, that the chief mode of action of ionizing irradiation is a direct cancerogenic action on the thyroid epithelium.

Since the report of Duffy and Fitzgerald in 1950,[6] the large number of confirmatory reports appear to leave no doubt of the cancerogenic effect on the thyroid gland of irradiation to the neck in infants and children. This relationship has been so clearly demonstrated that irradiation of the neck should never be employed in the young for benign conditions.

While no case of thyroid cancer considered to be due to the therapeutic use of I^{131} has yet been reported in an adult, Sheline, Lindsay and Bell[7] recently reported the development of three nodules, all considered to be true tumors, occurring 5 to 10 years after treatment of hyperthyroidism in patients under the age of 20. One of these nodules showed invasion through the capsule and was classed as an invasive adenoma or low-grade cancer. Not enough time has elapsed to provide any assurance that we may not yet see many thyroid cancers in adults treated with I^{131} after a longer latent period.

If the hypothesis of thyroid insufficiency and thyrotropic hormonal stimulation of the thyroid as a factor in the genesis of human thyroid cancer has any place in the effort to control this disease, its chief area of usefulness is clearly in the field of prevention. The evidence from the results of animal experiments and limited clinical experience is certainly sufficient to substantiate the use of desiccated thyroid in established or presumed hypothyroid states, of whatever cause, whether spontaneous or induced by known goitrogens, by partial thyroidectomy or by irradiation, as well as in cases of simple goiter or "borderline nodular goiters" in which surgery is not indicated.

From a practical point of view, the borderline nodular goiter is the crux of the problem which confronts the surgeon who must decide which nodular goiters require surgical removal.

The statistics concerning the relation of thyroid cancer to nodular goiter could hardly be more confusing. Much of this confusion, however, is purely semantic and the result of inaccurate communication and loose definition of terms. The confusion has been compounded by some who have sought to clarify it by bringing into the discussion statistics relating to the incidence of thyroid nodules undetected during life and found by serial section of the gland at autopsy. These data undoubtedly add to our total knowledge of thyroid disease but are of no help to the thyroidologist or surgeon who, confronted by a patient with a lump in his thyroid gland, must make a therapeutic decision. As Greene[8] has put it, "We can hardly concern ourselves as physicians with nodules the existence of which we are unaware."

There is wide variation in the reported incidence of thyroid cancer in relation to nodular goiter, depending on the manner of reporting; whether or not any known or suspected cancers are included in the total on which the ratio is calculated, and, in the case of the single nodule, depending as well on whether the calculation is based on single nodules as observed clinically or as determined at the operating table, or whether reported as the ratio of cancer to true single adenomas as determined by microscopic examination of the gland.

Taking all of these factors into consideration, it is our belief that unsuspected cancer will be found in approximately 4 per cent of patients operated on for nontoxic multinodular goiter and in about 6 per cent of patients with single nodules in whom clinical examination produces no reason to suspect cancer beyond the singularity of the nodule. This figure will rise to 25 per cent if later the number of cancers found is compared with the number of single true adenomas.

We are concerned here principally with the problem of premalignant lesions of the thyroid gland, but from a practical point of view it is impossible to discuss the treatment of these two possibly premalignant lesions without pointing out that in virtually every instance the overriding consideration is not the question of premalignancy but the question of the presence of cancer.

A surgeon may logically operate on a sin-

gle thyroid nodule which he believes to be an adenoma and premalignant, but if he cannot be sure that it is not already malignant—as he seldom can—he has a much more powerful reason for removing it.

With respect to the multinodular goiter, operation in the belief that the gland is precancerous is wholly illogical unless total thyroidectomy is done. But if 4 per cent of such glands are known to be cancerous, the decision must be based on this fact.

The crux of this problem, and the whole area of controversy, revolves around the definition of the nodular goiter. Opponents of the surgical treatment of nodular goiter cite the high incidence of the condition in the general population. They include in this category all goiters, from those barely palpable which show the slightest degree of unevenness of surface or lobulation in all shades and gradations to frankly knobby bosselated glands. There is without any doubt a wide "twilight zone" between the simple soft colloidal goiter and the nodular goiter of surgical significance. That there is a recognition of this—even in clinics in which the most aggressive views regarding the surgical treatment of nodular goiter are held—is borne out by the very modest number of operations reported for nodular goiter in comparison with the calculated incidence of goiter in such areas.

Unfortunately, it is not easy to define the nodular goiter of surgical significance. But with rare exceptions, all single thyroid nodules should be removed, especially in the young. With multinodular goiter, the presence of distinct firm nodules, 2.5 to 3 cm. in diameter, is enough to warrant consideration of surgical removal. The decision should be made by someone with judgment and a wide experience in the field.

Summary

Views regarding premalignant lesions and conditions of the thyroid gland must remain tentative to some degree, but the long-held belief in an association between nodular goiter and thyroid cancer has received support from the experimental production of goiters and thyroid tumors in studies on rats and mice.

The relationship of neoplasia in the experimental animal to stimulation of the thyroid gland by thyrotropic hormone induced by producing thyroid insufficiency with a variety of goitrogenic agents is well established. Tumors so produced are largely hormone-dependent and can be made to regress by feeding desiccated thyroid. There is substantial evidence that these same factors may play a part in the development of some thyroid cancers in the human. If this hypothesis is valid, the application of this knowledge in the prophylaxis against the development of cancer by the use of desiccated thyroid in all conditions of thyroid insufficiency offers great promise.

The cancerogenic effect of ionizing radiation of the thyroid gland in infancy and childhood appears to be established beyond doubt and its employment for benign conditions is contraindicated.

While the single thyroid nodule and the multinodular goiter may possibly be premalignant lesions, decision regarding surgical removal is rarely based on this possibility, but rather on the overriding question, which is nearly always present, of the actual presence of cancer.

REFERENCES

1. Graham, A.: Malignant tumors of the thyroid. Surg. Gynec. & Obst. 39:781-790 (December) 1924.
2. Wegelin, C.: Malignant disease of the thyroid gland and its relation to goiter in men and animals. Cancer Rev. 3:297-313 (July) 1928.
3. Greer, M. A. and Astwood, E. B.: Treatment of simple goiter with thyroid. J. Clin. Endocrinol. 13: 1312-1331 (November) 1953.
4. Crile, G., Jr.: The endocrine dependency of certain thyroid cancers and the danger that hypothyroidism may stimulate their growth. Cancer 10:1119-1137 (November-December) 1957.
5. Sloan, L. W.: Of the origin, characteristics and behavior of thyroid cancer. J. Clin. Endocrinol. 14: 1309-1335 (November) 1954.
6. Duffy, B. J. and Fitzgerald, P. J.: Thyroid cancer in childhood. Cancer 3:1018-1032 (November) 1950.
7. Sheline, G. E., Lindsay, S. and Bell, H. G.: The occurrence of thyroid nodules in children following therapy with radioiodine for hyperthyroidism. J. Clin. Endocrinol. 19:127-137 (January) 1959.
8. Greene, R.: Discrete nodules of the thyroid gland with special reference to carcinoma. Ann. Roy. Coll. Surgeons England 21:73-89 (August) 1957.

The Pigmented Mole

GEORGE T. PACK AND JEFF DAVIS

Memorial Center for Cancer and Allied Diseases, New York

Incidence and Etiology

GEORGE T. PACK

NEVI are probably all congenital. The term "acquired nevi," read often in dermatologic literature, is probably incorrect and has been based on the observation of nevi appearing for the first time in postnatal life. The time of origin of nevi and the time of their first visibility are not necessarily the same. Some moles in newborn infants are invisible at birth but appear after a variable time, perhaps after exposure has exerted its melanin-provoking influence. Moles acquire a much darker pigmentation during pregnancy, and women may even volunteer the information that "new" moles seemed to have occurred. The range of visibility for the human eye is rather narrow, and many tiny, faintly pigmented moles may not be seen under normal conditions. Some do become visible as pigmented lesions when the skin is examined in a dark room with the aid of Wood's light. This phenomenon may help to explain some unusual facts about malignant melanoma, e.g., the apparent development of malignant melanomas *de novo* at a site which had no precursory skin lesion, according to the patient, and the unusual instances in which metastases from malignant melanoma are found and treated, with the site of the primary melanoma remaining cryptic.

Allen has demonstrated pathologically the common origin of all melanomas from the junctional type of nevus, either alone or as a component of the compound nevus. The rare exception is a melanoma which occasionally arises from a blue nevus. Pack, Perzik and Scharnagel in a review of 951 cases of melanoma found that more than 50 per cent of their patients related a history of a pre-existing nevus.

Pack, Lenson and Gerber, utilizing a group of 1000 adult white patients who came to the Memorial Cancer Center for other complaints, noted the frequency and distribution of nevi in this group and prepared a scattergram representing the national incidence of nevi in adult white people. A total of 14,609 nevi were recognized on these 1000 people, an average of 14.6 moles per subject. Some people have more than a hundred moles and others have only two or three, but we have never examined a mature white adult who did not have at least one discernible mole. The very frequency of occurrence lulls suspicion and favors tolerance of these tumors by patients and physicians alike. Thus, while the incidence of

neurocnevi in the American population is very high that of melanoma is remarkably low, it being a relatively rare form of cancer.

The next survey attempted to discover how correct was our index of suspicion of moles which worried both patients and physicians enough to have specific moles surgically removed. A group of 840 patients had moles removed and microscopically identified as benign. A scattergram showed their regional distribution, which is only significant when compared with the natural distribution of moles in casual subjects and with the locations of malignant melanomas. In general, the percentage distribution of excised moles and malignant melanomas was almost identical for the skin of the trunk and upper extremities. Judging from comparative figures, there was apparently less and insufficient concern for nevi on the lower extremities and a disproportionate eagerness to have moles on the face excised; this last fact, in its true worth, might be due to a desire for cosmetic improvement by the removal of these conspicuous lesions rather than concern about the hazard of future malignant degeneration.

Regional Distribution of Nevi and Melanoma

This same study by Pack, Lenson and Gerber brought out some unusual facts about the regional location of these growths.

Nevi and melanoma of the eye—Melanoma of the conjunctiva is rare but does occur about as often as benign pigmented nevi in the same structure. We have seen congenital pigmented moles on the conjunctivae, more commonly near the internal or external canthus of the eye on developmental anomalies suggesting a primitive nictitating membrane. Except by comparison of character and rate of growth in our microscopic study over some time, it is extremely difficult to establish a differential diagnosis between some benign pigmented nevi found in the uveal tract and malignant melanomas.

Nevi and melanomas of the head and neck—Only 13.2 per cent of moles, as they occur in the general population, are situated in the skin of the head and neck, but 28.9 per cent of malignant melanomas are situated in this same regional distribution, indicating that the malignant tumor occurs twice as frequently as the benign tumor in a relative instance. Of benign nevi excised, 49.4 per cent were on the face and neck, indicating that their removal was more for cosmetic reasons than for fear of the hazard of malignant degeneration. The 31 malignant melanomas occurring in the oronasal cavity are only 2.5 per cent of the entire number seen and treated. Identifiable pigmented nevi are of extraordinary rarity in the mucosa of the mouth, oral cavity, and nasal accessory sinuses.

Genital moles and melanomas—In 1000 patients inspected for the detection of moles, with a total of 14,609 nevi in their skin, only 14 such moles were discovered on the skin of the genitals in both males and females. The regional distribution comprises only 0.1 per cent of all moles, as compared with relative frequency of melanomas, of which 35 or 2.8 per cent of 1,222 melanomas were in the skin of the male and female genitals. Two conclusions may be drawn from these figures; first, that the malignant melanoma is proportionately twice as common as is its benign prototype, the pigmented nevus, and secondly, that due to the relative infrequency of moles on the genital skin, they are predisposed to undergo malignant degeneration more often than moles in other locations. A natural corollary to this would be the wisdom of routine excision of all moles involving the genital skin as a proper prophylactic measure for the prevention of genital melanomas.

Anorectal moles and melanomas—Considering the thousands of proctoscopic examinations performed every year, it is surprising that pigmented nevi are not commonly found in the anorectal mucosa. It is indeed seldom that any are excised and studied microscopically for confirmation. This is unfortunate, inasmuch as it removes all opportunity for preventing anorectal melanomas. Of 1,222 cases of malignant melanomas in this series, 19 or 1 per cent were located in the anorectal mucosa. Melanoblasts are of some frequency in mucocutaneous junctions but seldom participate in forming congenital pigmented nevi.

Moles and melanomas of the extremities—A fact which we had long recognized clinically but which only recently had statistical proof was the disproportion of frequency of malignant melanomas on the lower extremities as compared with the upper extremities. Our study showed that 30.2 per cent of moles were situated in the skin of the upper extremities, whereas only 10.9 per cent of malignant melanomas were so located. Per contra, only 17.2 per cent of the pigmented moles were in the skin of the lower extremities, whereas 29.6 per cent of melanomas were in the skin of the lower extremities. Stated in another way, moles occur almost twice as frequently in the upper extremities as compared with the lower extremities, and melanomas occur almost three times as frequently on the lower extremities as compared with the upper extremities. Visible pigmented moles are infrequently encountered on the soles; only five such genuine moles (excluding other pigmented lesions) were identified on the 2000 soles of the 1000 patients, or a total of five of 14,609 moles generally distributed on these patients. If these figures have any significance, a wise precaution would be the routine removal of all pigmented moles found on the soles. The admonition we offer is constantly practiced by us.

Selective silver staining has shown that melanoblastic or melanotic whitlows are not infrequent, comprising 37 or 2.9 per cent of the malignant melanomas in this series. Pigmented nevi are not so often encountered in the nail bed and, when seen, should be surgically excised in their entirety in order to be available for microscopic study; in our experience, the melanoma occurs much more frequently in the nail bed than does the visible pigmented nevus. The advice to perform routine excision and microscopic study of these pigmented lesions of the nail bed is based on the clinical difficulty in establishing the differential diagnosis.

Sex and Age of Patients With Moles and Melanomas

Nevi are equally distributed among males and females. Pack, Perzik and Scharnagel found that 862 melanomas were almost equally divided between the sexes, not only as a group, but also in the various age groups. The majority of cases appeared in the 35 to 70 year period. The youngest patient was four months, the oldest 86 years. There was a female preponderance in the extremities and anorectal area, but this was not significant.

Unlike other types of cancers, melanomas do not have their highest incidence in old age. In this series there were 15 prepuberal melanomas. Of a total of 172 pigmented growths in children 12 years or younger which were suspected of being nevi or melanomas, McWhorter and Woolner, at the Mayo Clinic, found 11 growths which they classified as juvenile melanomas.

Race and Complexion of Patients With Moles and Melanomas

Pigmented moles and malignant melanomas are not commonly encountered in the darker races, such as the Negro and Mongol. Among 1,225 patients with malignant melanoma, Pack, Lenson and Gerber found only 17 Negroes, which is disproportionately few in view of the large Negro population in New York City. When melanoma does occur in the Negro, it is found with greater frequency on the soles of the feet, in the nail bed, and even in the oral mucosa, regions which commonly are not pigmented. Up to 1950, only 78 cases of melanoma in American Negroes had been reported in the literature. Melanomas have a greater incidence among African natives than American Negroes. Baxter reviewed 170 collected cases of melanoma among African Negroes. He re-emphasized the opinion expressed by other observers that in African natives the tumors frequently remain localized with less tendency to metastases and are less highly malignant, as demonstrated by their tendency to a more protracted course.

A study of the type and distribution of pigmented moles among peoples of the various races, including the Chinese, Filipinos, Indians (India), mestizos, Maoris, and pure-blooded American Indians of the Guarani tribe from the Chaco in Paraguay, showed a paucity of moles in these dark-skinned peoples, but a very great frequency in the mestizos of mixed

white and Indian blood. The majority of Negro patients with malignant melanoma are largely caucasoid in their appearance.

Myron Gordon has shown an experimental corollary to this clinical observation by mating the albino swordtail fish with the spotted platy, a closely related species which has micromelanophores. In the third generation—according to the Mendelian ratio—true malignant melanomas developed.

The majority of malignant melanomas occur in patients who are either extremely blond or have blue or hazel eyes and fair skin of delicate texture with so few melanoblasts that they burn rather than tan on exposure to sunlight. The second group in which melanomas occur with some frequency are those individuals who are redheaded or have a sandy complexion and who freckle on exposure to sunlight. It is estimated that only about 11 per cent of the American white population are of this coloration, yet more than 65 per cent of patients with malignant melanoma have this type of skin. It follows as a natural corollary, therefore, that it would be extremely important to remove all darkly pigmented moles, especially of the junctional type, as a prophylactic measure, in blond individuals of this coloration.

Classification and Diagnosis of Moles

General characteristics and natural history of nevi—Nevi are pigmented growths of the skin, mucosa and eye. They are essentially pigmented or, in some instances, nonpigmented malformations composed of atypical melanoblasts. All components of the integument may be involved in cutaneous nevi. At times, the epidermis, glands, hairs, blood vessels and connective tissue all may assume a secondary role.

The natural history of nevi runs a variable course. We have found, in examining the skin of 200 newborn infants, the incidence of pigmented nevi is 2.4 per cent, or 1 in 40 babies. This contrasts with the finding previously stated of 14.6 moles in each average adult. Obviously, then, nevi continue to appear for a variable time after birth and throughout adult life. Showers of new nevi are often reported by patients and are observed on examination in sites of the skin not previously involved. During pregnancy and at puberty, this is not uncommon. The growth which originally appears as a macular area of pigmentation may enlarge, change in color, configuration and size, or it may fade or remain arrested.

Nevi may be macular, papular, nodular, papillomatous or verrucous. Ordinarily, they vary in diameter from a few millimeters to a few centimeters. At times they may cover an entire section of the body surface, as in the congenital bathing-trunk nevi. Their color ranges from complete absence of pigment (amelanotic) through all shades of yellow, brown, black, and sometimes blue or purple. Hair may or may not be evident. The absence of pigment usually indicates that the growth is benign, though this is not an invariable rule. One or more lesions may occur on any portion of the body. The tumors vary in contour from linear to irregular configurations but generally are round to oval in outline. In most instances, they remain stationary and inactive for the remainder of life as a result of fibrotic changes that occur in their natural evolution and involution. However, they may grow slowly or become reactivated from various causes at any time of life.

Descriptive terms have been employed to indicate the various clinical morphologies of certain characteristically appearing growths. Thus, naevus spilus refers to a macular lesion, naevus pilosis to a hairy nevus, linear naevus to a nevus appearing to grow along the lines of blood vessels or nerve innervation, and cerebelliform mole to the type which has the appearance of cerebriform convolutions. These morphologic terms bear no relationship to the underlying microscopic findings. Certain nevi assume familiar clinical patterns. However, appearance does not offer an absolute means of making a histologic diagnosis any more than it does when one attempts to differentiate clinically between a basal cell and a squamous cell carcinoma of the skin without the final evaluation of microscopic study. In general, the fleshy raised tumors or the very deep-seated growths tend to be dermal nevi with or without a junctional component, while the su-

perficial flat growths are more often of the junction variety.

Nevi are classified in various ways. The most satisfactory classification appears to be determined by the position of the tumor cells in the tissue. Allen classifies nevi upon a histologic basis as follows:

1. Intradermal nevus
2. Junctional nevus
3. Compound nevus (containing dermal and junctional elements)
4. Blue nevus (Jadassohn-Tiéche)
5. Juvenile melanoma (herein termed prepuberal melanoma)

The intradermal nevus—This is the most ubiquitous of the nevi occurring on the skin. It accounts for at least 75 per cent of all nevi. In common usage, the term "mole" usually refers to the intradermal type of nevus, although it is also employed to indicate all types of pigmented tumors. The intradermal nevus is usually papular with a smooth or verrucous surface, or it may be papillomatous. It ranges from several millimeters to 1 cm. in diameter. In the large bathing-trunk type it reaches huge proportions. The brown color varies with the depth of the growth. This nevus is often somewhat of a paradox. Though anatomically it lies deep in the dermis, clinically it may appear to be quite superficial. Therefore, it can readily be mistaken at times for a junction nevus. Microscopic examination is frequently necessary to make the differentiation.

The majority of hairy nevi fall into this category. When hairs are present in a nevus, it is presumably of the intradermal type, but this is by no means pathognomonic. It may be located on any portion of the body, with the general exceptions of the palms, soles and genitalia. Junctional nevi usually occur on these sites.

The pure intradermal nevus, i.e., one without concomitant or junctional elements, is rarely seen before puberty. Its incidence increases with the onset of adult life and the reverse proportion then prevails.

The bathing-trunk type of nevus that involves the skin over extensive portions of the body is invariably of the dermal variety. Like other growths in this group, it is always benign unless it is associated in exceptional instances with a junctional portion which does not regress. Its removal may be indicated also for cosmetic reasons. The treatment is difficult because of its size. It usually requires a graft or multiple excisions in order to eradicate the growth.

The dermal nevus is essentially benign and rarely becomes malignant. When it does, it is combined with a junctional element in a portion of the growth and comes under the classification of a compound nevus. Such a differentiation must of necessity be microscopic.

The junctional nevus—The junctional nevus is the most important of the group because it possesses the inherent potentiality of changing to a malignant melanoma. The term "junctional" is appropriate because the vital element in its cellular structure occurs at the dermoepidermal junction. The growth appears as a smooth, hairless, flat macule or slightly raised papule, and it varies in color from light to dark brown or black. The superficial appearance of this nevus often belies its malignant possibilities. The majority of these nevi are relatively small. They vary in diameter from several millimeters to 2 cm. and are seldom larger. The junctional nevus may appear at birth or any time thereafter. The majority probably present themselves near the time of puberty and in early adult life. Often groups of new nevi suddenly appear over one or more portions of the body, particularly in early adolescence or at time of pregnancy. There are no particular sites of predilection on the skin, but those nevi occurring on the palmar and plantar surfaces, digits, genitalia and mucous membranes are almost always of the junction type. Because melanomas frequently occur in these sites, we advocate that junctional nevi located on these portions be routinely removed.

This growth cannot always be clinically distinguished from other types of nevi and, at times, from melanomas. It has been mistaken for pigmental basal cell carcinoma, angioma, histiocytoma, Kaposi's sarcoma, granuloma pyogenicum and other growths. In these instances, excisional biopsy is necessary to ascertain the correct diagnosis.

The junctional nevus has latent potentialities for change to any one of a number of dif-

ferent patterns; it may show retrogression, remain inactive, or actively evolve into either an intradermal or compound nevus, a juvenile melanoma, or be transformed into a true malignant melanoma. Ninety per cent of melanomas arise in junctional nevi. There may be a prolonged period of latency between the development of a junctional nevus and a demonstrable transformation into malignancy. The alteration may require many years. Thus, there is some element of the aging process in the evolution of malignant change. However, it does not equal that which exists in the degeneration of precancerous keratoses of the skin into carcinoma. In the latter, the incidence curve very closely parallels the increase in age, while in melanoma the greatest incidence occurs between the ages of 30 and 60, with no marked difference in the number during these later decades.

The rarity of melanomas indicates the paucity of instances in which the junction nevus is transformed into a malignant tumor.

The compound nevus—When a nevus is histologically composed of both a junctional and an intradermal element, it is termed a compound nevus. According to Allen and Spitz, 98 per cent of dermal nevi in adolescents are of the compound variety; but only 12 per cent in adults show the combined characteristics, because after puberty most dermal nevi lose their junctional component. These nevi are not clinically distinguishable from dermal nevi. Microscopic examination is necessary to identify their compound nature. Hairy nevi commonly are intradermal nevi. On rare occasions, they possess a junctional element, and then, like all compound nevi, they have the potentiality for malignant change to melanoma. Only a small percentage of melanomas arise from compound nevi. Of 362 melanomas, Allen and Spitz found 14 or 3.9 per cent to originate in compound nevi.

The erroneous impression that a "common mole" (intradermal nevus) can give rise to a melanoma rests on the fact that a dermal nevus which looks like an ordinary "mole" may have a junctional portion which contains the same potentiality for malignant transformation as does a pure junction nevus. For this reason, it is important to excise any dermal nevus that has shown evidence of change.

The blue nevus (Jadassohn-Tiéche)—The blue nevus originally described by Tiéche in 1906 had been recognized as a chromatophoroma by Riecke in 1903, and later as melanofibroma by Kreibich. However, it was not until approximately 1930 that there was clinical familiarity with or literary description of the tumor in this country and England.

Clinical description and diagnosis of the blue nevus. These tumors are blue, dark brown to black, blue-gray or an admixture of these colors which at times produces a mottled effect. The growths are slightly elevated, smooth, usually hairless papules or nodules varying from 2 to 15 mm. in diameter. The nevus occurs most frequently as an isolated growth over the face, forearms and dorsa of the hands. However, it may be found in most any other anatomic location, including the trunk, lower extremities, dorsa of the feet, wall of the chest, buttocks, scalp and bulbar conjunctiva.

The tumor may appear at any time of life. In all but four of Montgomery and Kahler's 65 cases, the growth was present at birth or since infancy. The ratio of females to males was 3:2. No racial predilection was noted. The tumors ceased to increase in size in early life.

Diagnosis of these tumors entirely on a basis of color is not warranted, as the growths frequently mimic the clinical appearance of a melanoma, and other nevi may assume similar coloring. A history of many years' duration without change is usually corroborative diagnosis of a blue nevus. In doubtful cases and particularly those in which the growth is apparently of recent origin, an excisional biopsy is indicated.

The blue nevus was formerly considered to be rare. However, the increasing familiarity of clinicians with this growth, and the greater number of specimens becoming available to the pathologist for microscopic examination have altered this belief. Montgomery and Kahler have also expressed the opinion that its incidence is not low.

Malignant variant of the blue nevus. The blue nevus is a benign growth which seldom

undergoes malignant change. The deep color and the microscopic picture of the benign blue nevus are easily confused with the true melanoma. Its dark color is created chiefly by its relatively deep position in the dermis. Histologic examination occasionally gives evidence of an associated intradermal or junction type nevus. Authentic cases of malignant degeneration of a blue nevus have appeared in the literature. Such a diagnosis of a melanoma arising from a blue nevus must be accepted only after careful consideration of the clinical and pathologic findings. In some instances, highly cellular and extensively pigmented blue nevi may closely resemble a melanoma on pathologic examination. In other cases, a spindle-cell melanoma or spindle-cell melanotic metastases may be mistaken for the degeneration of a blue nevus. In our personal series there have been several cases of metastasizing malignant blue nevi, one patient living and well for more than a decade.

Differential diagnosis of blue nevus. The blue nevus has been most frequently confused with the Mongolian spot. This is a solitary, nonelevated, nonindurated, smooth, brown to blue, pigmented plaque of 2 to 12 cm. in diameter that usually occurs in the sacral region. As a rule it is present at birth and disappears spontaneously within several years. Multiple plaques are rare, but may occur over other portions of the body. It occurs in the Caucasian race, as well as in the Mongolian.

The blue nevus may at times resemble other nevi, dermatofibroma (histiocytoma), minute deep-seated angiomas or melanoma. The firm consistency and typical bluish color are distinguishing characteristics of the blue nevus, sufficient to differentiate it from other nevi or melanoma. Small deep angiomas may resemble blue nevi in coloring but are soft on palpation, and blood may be withdrawn on insertion of a needle into the tumor. When the tumor resembles a melanoma and the history of the time element is vague, or when the diagnosis is in doubt, excisional biopsy is indicated.

Prepuberal melanomas—Development of the concept of prepuberal melanoma. There is an important type of pigmented nevus which bears such a close resemblance to malignant melanoma that it is usually not possible clinically to distinguish between the two. This nevus may be found in children from the age of one to the time of puberty. When this tumor is excised in infancy or childhood and submitted to pathologists for diagnosis, they are sometimes unable to say whether the neoplasm is benign or malignant, inasmuch as the histologic criteria, exclusive of invasion and permeation of vessels, are practically similar to the malignant variety of melanoma as encountered in adults. Even though the tumor has structurally the conformation of the true melanoma, it ordinarily does not behave as such until after puberty. Although there have been instances reported in the literature, and several juvenile patients in our series have died of metastasizing melanoma, this manner of behavior is rare and certainly not the rule. This fact is now so well recognized that pathologists insist on having clinical information available concerning the age of the individual, and whether or not evidences of approaching puberty exist.

In 1939 one of us originally proposed the concept that so-called melanomas of childhood tend to follow a benign course and seldom metastasize. We stressed the probability of hormonal influences inhibiting malignant melanomas during childhood and stimulating them to active malignancy after the onset of puberty. Some few years later, additional reports in the literature by Pack, Sylven, Webster, Stevenson and Stout gave further confirmation of this concept. In 1948 we suggested the term "prepuberal melanoma" for these tumors which were clinically differentiated from adult melanoma because of their usual benign behavior during adolescence, but which were usually histologically indistinguishable from melanomas. Shortly thereafter, Spitz proposed the term "juvenile melanomas" and presented histologic differences by which they could be separated from adult melanomas in about half the cases. In this series and that of Allen and Spitz and Williams, cases of fatal malignant melanoma in childhood were presented. Allen and Spitz came to the conclusion that growths previously considered to be the benign childhood type of malignant melanomas, because of

their benign course and designated histologically by them as juvenile melanomas, were definite histologic entities, quite separate and distinct from adult malignant melanomas. Similar lesions having the same histologic appearance were also observed in adults and found to pursue a subsequent benign course.

Thus it became apparent that there was a growth (prepuberal or juvenile melanoma) occurring in childhood and in an occasional adult, the histology of which resembled a true malignant melanoma, but which clinically pursued an entirely benign course. At the same time there were true malignant melanomas occurring in childhood, though rarely before puberty, with consequent metastatic extension and death. When they do occur, they are not histologically different from adult melanoma. Out of this seeming chaos, the prepuberal melanoma has now been properly classified as a particular type of benign pigmented nevus, having the potentiality of melanomatous transformation with the advent of puberty.

Clinical description of the prepuberal melanoma. Prepuberal melanomas may present themselves at any time during childhood from infancy up to the onset of puberty. They are also occasionally seen in adults. These nevi are often lightly pigmented shades of pink to red or light brown to blue or black in color. The more vascular tumors have a reddish hue. They are papular to nodular tumors with slight to marked elevation and vary from several millimeters to as much as 3 cm. in diameter. The tumors may be sharply marginated or irregular in outline. In most instances the surface is smooth but it may be verrucous. They are invariably hairless. There seems to be no sex predominance. A major portion of the lesions occur about the trunk and the upper and lower extremities, including the dorsa of the feet. When the child is presented for examination, there is a history of duration from the life of the child to as short as five or six weeks. Their most characteristic and universal feature is a history of increase in growth. This is a gradual increase in size, except in the rare case where rapid growth has been known to take place.

There is a general misconception that a histologic differentiation cannot be accomplished between benign prepuberal melanoma and true malignant melanoma in children. Furthermore, there has also been an erroneous assumption that malignant melanomas, if they occurred at all in children, did so with such rare frequency as to be of no practical consequence. Hence, in many instances the pathologic diagnosis of a true malignant melanoma in a child conveyed no serious import to the surgeon but was responsible for dire results in certain cases.

Spitz described definite histologic characteristics prerequisite for the diagnosis of prepuberal melanomas as well as establishing histologic features that enable a differentiation between the benign prepuberal melanomas and the true malignant melanoma of childhood.

According to Allen, Spitz's criteria for the diagnosis of benign prepuberal melanoma include: "edema, lymphangiectasia and telangiectasia, hyalinization of the upper cutis; certain forms of giant cells; relatively bland and interrupted junctional change; pseudoepitheliomatous hyperplasia; large discrete, epitheliumlike clusters of round, polygonal or spindled cells within the upper dermis commonly associated with collections of lymphocytes and histiocytes; and finally, a paucity of melanin pigment in the vast majority of lesions.

"The diagnosis of the melanocarcinoma is based predominantly on the absence of the aforementioned landmarks of the juvenile melanomas and on the presence of an aggressive histologic appearance of both the intradermal and epidermal components." In addition there is an accentuated activity in the area of epidermal junctional change with occasional anaplastic cells present in the epidermis.

Incidence—Hormonal influence and malignancy of prepuberal melanoma. Prepuberal melanomas fortunately are rare. Of 100 specimens of pigmented nevi in children examined by Spitz, there were eight prepuberal melanomas. Of 13 cases of prepuberal melanoma there was one fatal case in a girl 12 years of age, with inguinal lymph nodal metastases. The malignant variant of prepuberal melanoma may not necessarily be attended by the same fatal prognosis as in adults. Webster,

Stevenson and Stout followed an eight year old child for 12 years after excision of a juvenile melanoma of the skin of the shoulder and dissection of cervical metastases. As is well known this variance in the malignant behavior pattern is occasionally experienced for melanomas in adults.

As the incidence of prepuberal melanomas markedly decreases after puberty and is relatively infrequent after the age of 40, it is considered possible that, like compound nevi, they assume the histologic structure of intradermal nevi after puberty.

Morphologic studies have offered no evidence to account for the clinically benign behavior of these histologically malignant tumors. Evidence has previously been presented, however, of the stimulative effect of puberty on the growth activity of nevi and changes in their cellular and pigmentary constituents. Likewise, the malignancy of persisting prepuberal melanomas may sometimes become established when puberty supervenes. Prior to puberty, an inhibitory mechanism, presumably of a hormonal nature, seems capable of depressing the systemic dissemination.

Prepuberal melanomas in adults. The course of prepuberal melanomas in certain respects resembles that of compound nevi. As some compound nevi in childhood continue with an unaltered histologic structure, so certain prepuberal melanomas retain their junctional component in adult life. Since prepuberal melanomas are rare after the age of 40, it is thought that most of these growths are transformed into an intradermal nevus at or about the onset of puberty. However, the fact that some melanomas show microscopic evidence of a prepuberal melanoma having existed should be sufficient evidence to regard these growths as potentially premalignant.

The significant conclusion to be drawn from these observations is the obvious necessity for complete surgical removal of all dark, deeply pigmented nevi in infancy and childhood. Their removal at this time of life entails only minor surgical procedures without the hazards of recurrence. Increase in size, evidence of growth, elevation or increased pigmentation and change in color are all suggestive of prepuberal melanoma. Since the neval element in these growths does not extend beyond the margin of the growth or deeply into the subcutis, radical excision is not mandatory. It is a serious mistake, however, to delay this operation until evident change has occurred in the appearance of the tumor, particularly if the change develops at the time of or shortly after puberty.

Transformation of Benign Nevi Into Malignant Melanoma

It is now well authenticated that all melanomas of skin and mucous membranes arise from a junctional or a compound nevus. The only exception is the rare instance of the malignant transformation of a blue nevus. Junctional and compound nevi are not malignant per se, nor do they contain melanomatous elements; they only have the potentiality of malignant transformation. Thus, they are precancerous or premelanomatous growths. That melanomatous change supervenes in only a minute percentage of cases is apparent from the omnipresence of these tumors, and at the same time the relatively low incidence of melanomas. Not only is the junctional nevus which shows microscopic evidence of activity a candidate for malignant transformation, but the quiescent junctional nevus may on occasion eventuate into a melanoma. Allen and Spitz stated that "in those restive junctional nevi which are anaplastic and in which certain qualitative cellular changes have occurred, the odds are enormous that this altered junctional nevus, if allowed to remain, in time would evolve into a melanocarcinoma." As yet, there is no means of determining which growth will actually exhibit malignant change.

The concept is no longer tenable that other pigmented nevi, including the intradermal nevus or common mole, are capable of transformation to melanoma. As has been stated, the one exception is the blue nevus which occasionally does so. When dermal nevi degenerate into melanoma, there is a junctional element present in the growths and the lesions are actually compound nevi.

Hairy nevi—It has been a widely accepted principle that hairy nevi never undergo mela-

nomatous change. In general, this rule is reliable since most hairy nevi are usually of dermal variety, therefore, not prone to malignant change. However, a junction nevus located on a hairy portion of the body may on occasion contain a hairy element. Recently, Woodburne and his associates observed a hairy mole on the shoulder of a 28 year old man, which on pathologic examination proved to be an early melanoma.

The controversial role of trauma in the malignant transformation of moles—There has been considerable forensic interest in the reputed role of trauma in converting benign pigmented nevi into malignant melanomas. It seems unlikely that a single injury to normal skin could induce the onset of a tumor so highly complicated as a nevus or a malignant melanoma. A report from Africa stated that Sudanese natives had been seen with malignant melanomas on the soles of their feet. These growths were attributed to an irritating thorn which commonly became implanted in the soles. In America, accumulated case histories have suggested that repeated chronic irritation of pre-existing nevi could be a factor in inducing their change to malignant melanomas, particularly when the nevi are found on regions subjected to frequent and constant pressure such as the neck, arms, groin, feet and genitals. More than half the cases of melanoma in which trauma was considered a factor occurred on the feet, in the cases reported by Gleane, Amadon, Coley and Hoquet, Stevenson, Klauder, Hazen and Farrell.

It is pertinent in the discussion that the proportion of melanoma occurring on the hands, feet and genitalia is relatively high, although the occurrence of pigmented nevi in these sites is relatively uncommon. This higher incidence of transformation of nevi into melanomas in these sites may be explained by the fact that the growths in these locations are almost always of the junction or compound variety. Thus, while nevi of the hands, feet and genitalia are, for the most part, either junctional or composed of junctional elements, the overall percentage of this type of nevus of the skin of the rest of the body in an adult is proportionally small.

A recent careful review of patients' histories would indicate that trauma was alleged to have initiated changes in not over one-fifth of our patients. Even this was a doubtful factor in most instances, because the trauma appeared to be insignificant and probably served only to focus the patient's attention to the mole which was already beginning to show malignant change. Malignant melanomas are not significantly frequent on the neck and waist, that is to say, along the collar and belt lines where pressure is constantly applied. The trauma of shaving does not appreciably alter the incidence of melanomas on the face, as judged by their proportion of occurrence in males and females. The ordinary mole is not a fragile structure, but the malignant melanoma is, and in consequence of its fragility, soft texture and vascularity, it is easily and repeatedly injured, resulting in early bleeding and ulceration. Reputed instances in which trauma is said to have caused the conversion of a benign nevus into a malignant melanoma, on critical inquiry, leave considerable doubt as to whether the tumor originally was a nevus or an early melanoma. We are inclined to the viewpoint that the histologic character of the mole, for example a junctional nevus, is of infinitely greater importance in determining the possible conversion to the malignant tumor than is the accident of injury.

The fear of trauma has created some difference of opinion as to the advisability of removing tissue from a nevus for biopsy. It is believed by some that this may be responsible for stimulating a nevus into growth activity. Nevi are commonly of such proportions that excisional biopsies may be performed. When an extensive nevus is present and complete removal would entail the excision of a great amount of tissue or cause disfigurement, a biopsy would be of paramount importance in order to ascertain whether or not complete removal of the lesion was necessary. In the few instances where such a biopsy is indicated, it is believed that there is little possibility of dissemination of tumor emboli. This gains confirmation in the opinions expressed by Ewing, Wood, Boyd and Mackee.

Many laymen and, unfortunately, some phy-

sicians erroneously believe that one should never remove a pigmented nevus unless it bothers the individual who has it because it might result in the production of a melanoma. This is a dangerous doctrine. When a pigmented nevus begins to trouble the patient, it usually means that a melanoma has already developed. The physician may excise what he believes to be a benign nevus and will perform this operation in a conservative fashion in the office without a microscopic study of the specimen, only to be chagrined later to have the patient return with evidences of regional and distant dissemination. If a pigmented nevus is completely removed during its benign state, it never recurs as a melanoma. The local recurrence of a melanotic tumor or the appearance of metastases in regional nodes or distant viscera after conservative removal of a supposedly benign nevus indicates that the original tumor was already malignant but unrecognized as such at the time of the conservative excision. This offers a strong argument for routine microscopic study of every pigmented nevus that is excised.

Hormonal Influence on Moles and Melanoma

The groups of neval cells constituting this congenital tumor may be invisible evidence at birth, particularly in the very large lesions such as the bathing-trunk nevi. The coloration of these tumors, however, seems to proceed after birth with exposure to light; in other words, the elaboration of the pigment does not seem to occur greatly in utero. Many of them do not increase in dimension except proportionately with the rate of growth of the child. It is evident in studying the phenomena of the development of pigmented nevi that many of them are not visible until after the onset of puberty. A child with a few scattered pigmented moles here and there may, in company with the endocrine changes attendant on the state of puberty, have the rather sudden development of numerous pigmented nevi over the skin of the face, trunk and extremities. It is assumed that these are not new growths in the strict sense of the word, but that the neval cells may have been present but unrecognized until influenced by the hormonal factors which increase at this time.

Many parents have brought for examination children between the ages of 10 and 14, in considerable apprehension because of the sudden appearance of numerous dark moles previously unnoticed or inconspicuous. With approaching pubescence, pre-existing moles commonly change to become larger, darker and more elevated; furthermore, other moles invisible or faintly seen show increased pigmentary changes. These observations would support the thesis that the pigmented nevus is extraordinarily sensitive to the stimulating hormonal influence of the pituitary, adrenals and gonads. We have had the heartbreaking experience of treating too many young girls and boys aged 14 to 20 years with malignant melanomas that could have been prevented by the prophylactic excision of benign precursory nevi in childhood.

It is our belief that the malignant melanoma, in its derivative from the pigmented nevus, is a tumor closely related to the endocrine system and markedly influenced by the activity of the endocrines, notably the gonads, the suprarenal cortex, and the hypophysis. In keeping with this opinion, we have observed malignant melanomas to occur in adolescent girls and boys just after the age of puberty.

The moles of pregnant women become darker during the pregnant state. The tendency for moles to become malignant during pregnancy may be three times as great as during other periods of life, although this is very difficult to prove by control series. In comparable series of pregnant and nonpregnant women with melanomas, more of the pregnant women (30 per cent more) appear with metastases to regional nodes than in the nonpregnant group, but the five year definitive cure rate is approximately the same for the two groups, when it is analyzed according to the stage of the disease.

Another phenomenon which may be the result of hormonal influence is the evident activation of multiple junction nevi in patients who have actively growing melanomas. The study of such excised moles bears testimony to the activity of these coexistent nevi. This

association may explain the multicentricity of primary melanomas in some patients.

Inheritance of Moles

There is abundant experimental evidence to indicate the hereditary occurrence of malignant melanomas in animals. The hereditary genetic aspects of melanomas in animals have been demonstrated in numerous animal species: in the hybrid fishes by Gordon; *Drosophila* by Burdette; exolotls (salamanders) by Sheremetiena and Brunst; mice by Cloudman; female pine snakes by Ball; swine by Caylor and Schlotthauer; gray horses by Brugnone, Gohrer, Virchow and Van Dorssen.

The familial occurrence of human melanoma has also been repeatedly confirmed. Ocular melanomas occurring in successive members of one family have been observed by Davenport, Silcock, Pfingst, Parker and Stokes, and Waardenburg. Cawly recently reviewed the genetic aspects of melanoma and reported melanoma occurring in a father, son and daughter. We have had four families in which familial occurrence of malignant melanoma was observed.

New Experimental Approaches to Differentiate Between Nevi and Melanomas

The exact physiologic processes involved in the transformation of a quiescent junctional nevus into a rabid growth is unknown. However, the important role of the endocrines as stimulating elements in this transformation has been previously related. This pronounced influence of hormonal secretions is perhaps even more striking in the critical stage during which a benign nevus changes to a malignant melanoma.

It is not always possible to observe by clinical means the transformation of a pigmented nevus into a malignant melanoma. Frequently only histologic examination reveals the junctional nevoid origin of a melanoma. A patient with evidence of melanomatous metastasis to regional lymph nodes may present a closely adjacent pigmented nevus which clinically appears to be perfectly innocuous. Only when such a tumor is excised does the pathology indicate that the tumor is a true melanoma. When a pigmented nevus that has long been quiescent undergoes certain changes, such as becoming more elevated, with increased pigmentation or with ulceration, bleeding and localized discomfort or pain, it may indicate that the tumor is becoming malignant.

The determination of the point at which a junction nevus has changed to a melanoma in a recent small lesion may also pose a difficult problem from the pathologist's standpoint. The recent histochemical technics developed by Fitzpatrick offer a new approach to this dilemma. He has demonstrated that of the malignant neoplasms, melanoma cells alone are capable of forming melanin when incubated in tyrosine, while nonmalignant pigmented cells in normal skin require activation of the tyrosinase system by an additional stimulating factor, such as ultraviolet light, in order to form melanin when incubating in tyrosine. By this means, benign junction nevi have been differentiated from melanomas.

Cawley, Rathbun and Wheeler made infrared spectroscopic studies of pigmented tumors, including nevi and melanoma. The pigmented skin tumors were examined in the infrared transmission and absorption of these growths in the region of 2 to 16 μ. The infrared spectrums of the pigmented tumors showed dissimilarities of absorption intensity could be correlated with differences in concentration of the nucleic acid content of various tumors (phosphoric acid and pentose constituents). In general, it appeared to the authors that malignant melanoma, both primary as well as those metastatic to the skin, contained more nucleic acid compounds than any of the nevi or other pigmented tumors examined.

General Management of Pigmented Moles

The removal of all moles of suspicious or dangerous character should be done in infancy or childhood, before the possibility of malignant transformation can occur. In some instances, the melanoma appears to develop from otherwise intact skin and would, therefore, be melanoma *de novo*; yet we cannot state with certainty that neval cells do not pre-exist, as

they may not have been in a cluster sufficiently large or with sufficient pigmentation to be obvious to our vision. Under such circumstances it is conceivable, although one cannot prove it, that a nevus of microscopic size may have been present. The metastatic dissemination of malignant melanoma to regional lymph nodes may occur from an adjacent pigmented skin tumor that has all the appearance of benignity. On the other hand, if a long-existent, pigmented mole that has not changed its character suddenly becomes elevated, increasingly pigmented, ulcerated or bleeds and is attended by localized discomfort or pain, one may assume, until proved otherwise, that a malignant melanoma is in the process of formation.

All nevi which are of a suspicious type or showing change should be surgically excised with considerable margin, and the specimen always referred to a competent tumor pathologist for microscopic study. It has not been unusual to see patients whose moles were pronounced benign by pathologists, only to have metastatic melanoma appear in regional lymph nodes at a later date. This tragic occurrence necessitates a review of the original microscopic sections and a change in the diagnosis. A routine microscopic study of every excised pigmented mole should be done. The excision in all instances may be conservative, but if malignant melanoma is found, hospital admission with radical surgical treatment becomes imperative.

Huge congenital nevi that cover a large expanse of skin should be excised in childhood before the prepuberal period. This may be done by repeated segmental excisions, removing the central portion of the tumor as widely as possible each time and allowing for the elasticity of the skin to permit another wide central excision at a later date, until only a linear scar is left or, if feasible, applying a skin graft.

The general principles of management and treatment of nevi as well as indications for their prophylactic removal are fully presented in articles on the subject by Pack and Davis. The principles of treatment which are embodied in these studies are summarized in the following outline:

TREATMENT OF NEVI

Indications for Prophylactic Removal of Nevi

1. When a nevus on any portion of the skin is subject to repeated irritation and infection.
2. When a nevus shows any evidence of change, and particularly if there is:
   a. Increased pigmentation.
   b. Increase in size or contour.
   c. Inflammatory reaction in or about the nevus.
   d. Ulceration, bleeding, crusting (late signs).
   e. Pain or discomfort.
3. All apparent junctional nevi on the genitals, hands, feet and mucous membranes.
4. All nevi that are any shade of blue or black.
5. Changes that occur in nevi that have appeared late in life should arouse special suspicion.
6. Decision as to removal should not be made on the presence or absence of hair in a nevus. In general, hairy nevi are not the pathologic variety which give rise to melanoma, but this is not an invariable rule.
7. In extensive nevi covering a large skin surface where decision as to removal depends on consideration of the pathologic type, biopsy is permissible.
8. Juvenile or prepuberal melanoma may not appear to be benign. Increase in size or deepening in pigmentation may be the only clinical signs of their character. Therefore, any nevus in a child before adolescence that demonstrates such changes should be surgically excised.
9. Deeply pigmented nevi in blond, redheaded and freckled patients may well be removed as prophylactic measures.
10. Darkening nevi and nevi of changing aspects during pregnancy may well be removed as a precaution.

Definitive Treatment of Nevi

1. Surgical excision under local anesthesia is the appropriate method of treatment.
2. Nevi, like melanomas, are radioresistant; therefore x-ray or radium is never employed for their treatment.
3. Partial biopsy is never indicated in lesions small enough to be entirely removed at the time of the surgical procedure.
4. The excision should be wide enough to accomplish complete removal of all pigment-containing cells both in depth and at the border of the lesion.
5. Electrodesiccation or cryotherapy of nevi is hazardous because:
   a. Biopsy is usually not made available.
   b. Removal by electrodesiccation may be too superficial, allowing some neval cells of the tumor to remain.
   c. If a portion of a nevus remains after electrocautery, this partial procedure may be followed by rapid regrowth of benign or malignant character.
6. In fairness to the patient, all specimens should have the benefit of a pathologic examination regardless of the clinical diagnosis.
7. Whenever feasible, all patients having a surgical excision for a nevus of any type should have the wound re-examined after a reasonable interval for evidence of residual pigmentation or development of keloid formation.
8. Extensive bathing-trunk types of nevi are treated by surgical excision and plastic repair. The skin is undermined sufficiently to effect primary wound closure either by sliding flaps or by skin grafting.

Clinical Staging and Proper End-results Reporting of Cancer

R. LEE CLARK, JR.*

The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston

R. LEE CLARK, JR.

STUDENTS of the cancer problem have long recognized the need for consistency in evaluating results of treatment of cancer in order to compare their methods and technics with those of others. To accomplish this, it is necessary to separate individuals with a specific type of cancer into groups according to the extent of disease at the time they came for treatment. This separation of cancer cases into categories according to an agreed plan is known as "staging." The "stage" is the apparent extent of disease when the patient is examined clinically. Recognition of the need for staging has paralleled improvement in knowledge of the disease, with development of a more specific definition of site, histology, and routes of metastases.

*Director, The University of Texas M. D. Anderson Hospital and Tumor Institute; Professor of Surgery, The University of Texas Postgraduate School of Medicine, Houston, Texas.

Staging criteria must be universally known, generally accepted, and routinely used in reporting end results of treatment. Only then can the information available in the vast laboratory of records of cancer patients be reduced to usable proportions to permit the understanding and sharing of factors in various kinds of therapy and prognosis. Study of such comparisons will eventually result in clarification of the type of treatment which will be most meaningful. The individual physician, faced with a stated set of conditions, will thus have available a rational plan of action. There have been various proponents of staging for cancer of other body sites but acceptance of any one classification has not been achieved. Lesions of the breast have been of particular interest and have been classified by many different systems. However, the painstaking studies required to arrive at a staging system that is likely to be adopted internationally have only recently been undertaken.

The value in the standardization of "end results" reporting has been well demonstrated. One example of such a demonstration was when the American Radium Society, celebrat-

ing the fiftieth anniversary of the discovery of radium in 1948, had guest speakers from most of the centers of the world treating cancer patients. Of particular interest was a panel discussion on cancer of the tongue. Every member of the panel sent his total data well ahead of the meeting to the president of the Society. These were uniformly prepared and presented by Macdonald[1] according to "standard criteria for reporting end results." With the figures thus prepared it was possible to compare the results of different methods of treatment in cancer of the tongue from various cancer centers. This was an important demonstration of the possibility of detecting a "norm" for the results of treatment of cancer of a given anatomic site. Results above or below this norm indicated need for appraisal; in the one case to find out the reason for a better result so that it could be generally applied; in the second, to improve methods to raise results to the norm. This interest of the members of the American Radium Society was reflected in an action by the American College of Surgeons in the appointment of a committee from that organization to study an approach to consistency in the reporting of end results. In 1958, a committee was organized to include representatives of the American College of Surgeons, College of American Pathologists, American College of Radiology, American College of Physicians, American Cancer Society, and National Cancer Institute, among whom general unanimity was reached.

In 1952 the Committee on Tumor Nomenclature and Statistics of the International Cancer Research Commission recommended that work on a code for the clinical staging of carcinoma be initially confined to accessible sites. Committee members also agreed that criteria for this purpose be limited to information obtained from the physical examination, supplemented by "such instrumentation as is in general use by the practitioner and not such as to require consultation with a specialist."[2] Since this precludes biopsy, it has been one of the chief obstacles to more widespread acceptance of these staging criteria. Many authorities believe that staging of cancer in such areas as the uterine cervix or breast should be done with the best evidence available, including histologic study.

A number of international medical organizations have been interested in this problem, including the World Health Organization and the International Congress on Radiology. Since 1954 the responsibility has been assumed by the Research Commission of the International Union Against Cancer to draft precise classification for cancer of the breast, cervix uteri and larynx and to extend the general technic to cancer of certain other sites.

The Research Commission has appointed a committee to carry out these objectives, termed the Committee on Clinical Stage Classification and Applied Statistics (C.C.S.C.A.S.).*

The objectives of classification, as outlined by the committee, are:

1. Precise clinical description and classification of malignant neoplasms to (a) aid the clinician in the planning of treatment, (b) give some indication of prognosis, (c) assist in the evaluation of results of treatment, (d) facilitate the exchange of information between treatment centers, and (e) assist in continuing investigation of human cancer.

2. The principal purpose to be served by international agreement on some formal plan of clinical description and classification of malignant neoplasms is to provide a method of conveying experience to others. Any such system should be simple, practical, and capable of revision or adaptation to meet changing requirements. It should also be adaptable to statistical analysis and mechanical tabulation.

In 1958 the American College of Surgeons authorized its Cancer Committee to arrange for a joint study of this problem with the American College of Radiology by inviting the medical groups most interested in the care of

*The committee is composed of the following representatives: pathologist: Dr. Hamperl (Germany); surgeons: Dr. M. M. Copeland (U.S.A.), Dr. P. F. Denoix, chairman (France), Dr. E. Lima-Basto (Portugal), Dr. A. I. Racov (U.S.S.R.), Dr. A. W. Fischer (Germany), Dr. M. Harmar (England), and Dr. P. Bucalossi (Italy); radiologists: Dr. F. Baclesse (France), Dr. E. Barajas-Vallejo (Mexico), Dr. Sven Hultberg (Sweden), Dr. M. O. Roxo-Nobre, secretary (Brazil), and Dr. R. McWhirter (Great Britain); statisticians: Dr. W. P. D. Logan (Great Britain) and Dr. A. H. Sellers (Canada).

the cancer patient in the United States to participate. Thus, the U.S.A. Joint Committee of Cancer Staging and End Results Reporting was formed by representatives from the American College of Surgeons, American College of Radiology, College of American Pathologists, American College of Physicians, National Cancer Institute, and the American Cancer Society. The Joint Committee has received financial aid from the American Cancer Society and the National Cancer Institute. Dr. Murray M. Copeland is its chairman. The cooperation and best judgment of these various groups were assured in this endeavor to effect most rapidly an international language in malignant disease.

From the research of these several committees, a staging method called the TNM system has evolved.[3] The three letters refer, respectively, to "*t*umor," "regional lymph *n*odes," and "distant *m*etastases." The staging plan, devised by a committee of 13 members from 11 countries, under the chairmanship of Dr. P. F. Denoix of France, was accepted by the International Committee for Stage Grouping and the Presentation of End Results.[3] With the support of the International Union Against Cancer, the TNM system will (it is hoped) be adopted by the World Health Organization. It is based on two principles:

1. Identification of cases in the study group by local extension of the primary tumor (T), the status of regional lymph node involvement (N), and presence of distant metastases (M).

2. Establishment of conventional stages (usually four) by grouping cases according to extent of tumor, status of regional lymph node involvement, and presence of distant metastases. This critical step indicates the status of the lesion that is important with respect to both prognosis and treatment. Also, the particular characteristics defined according to site will lead to a comparison of end results among different institutions.

The TNM system as it presently stands has limitations in the classification by stage of deep-seated or disseminated tumors. Each anatomic site must be studied and its peculiarities defined and agreed on before the general plan of staging can be adopted. However, once the clinician learns the basic rules, he has only to acquire knowledge of the modifications necessary for the specific anatomic site under consideration. In general, the lesions immediately amenable to staging by this method are the accessible ones, which include cancer of the lip, mouth, larynx, skin, uterine cervix and breast.

Principles of the System

In classification, adherence to exact definitions of T, N and M is of the utmost importance. Complete and accurately compiled case records will facilitate logical staging. Extent of the primary tumor is expressed in four degrees: T-1, T-2, T-3 and T-4. Although explicit definitions for these categories will depend on the site of the growth, the following generalizations for all sites may be made:[3]

T-1 is a relatively small tumor limited to the organ of origin.

T-2 is a larger tumor confined to, or with slight extension beyond, the point of origin.

T-3 is a tumor which infiltrates the adjacent structures.

T-4 is a tumor with widespread involvement of adjacent structures.

The status of the regional lymph nodes is recorded in three degrees:

N-O indicates that no nodes are palpable.

N-1 indicates that regional lymph nodes are palpable but movable.

N-2 indicates that regional lymph nodes are fixed or matted together.

N-x indicates that regional lymph nodes are not accessible and cannot be visualized.

Certain difficulties are inherent in this part of the classification system with relation to specific areas. Regional lymph nodes may not be palpable for some primary tumors as, for example, in cancer of the bladder or rectum. In other instances, as in cancer of the breast, some regional lymph nodes can be palpated but others cannot. Another problem is to determine whether the lymph node is normal or whether it has been invaded by tumor. This is finally a matter of opinion of the examining physician, and is influenced by his training and the number of patients he has examined, as well as by such factors as the ease with

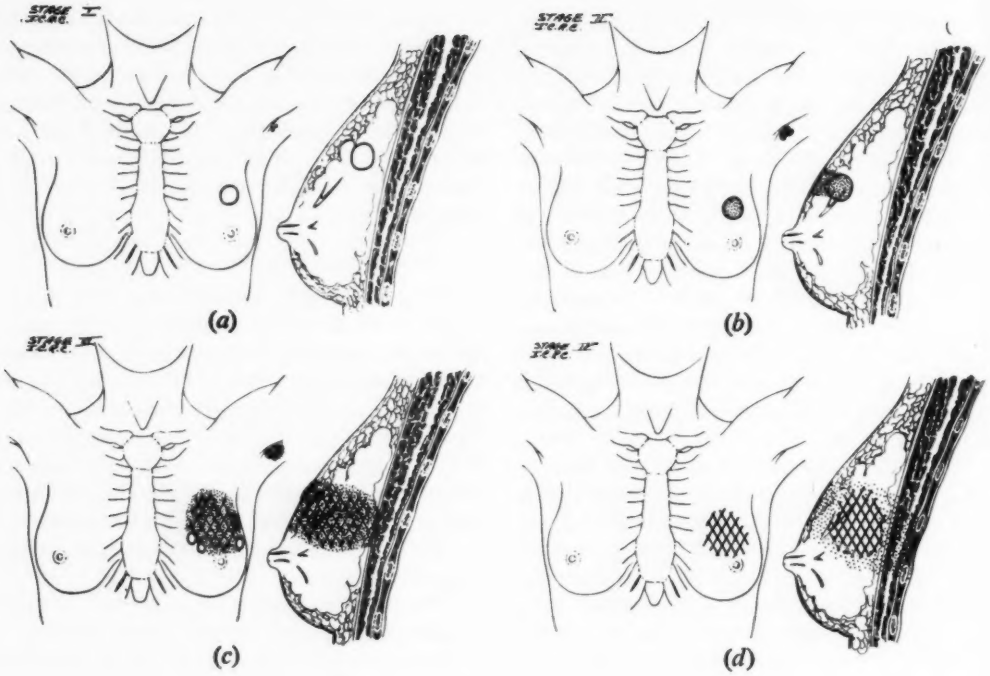


FIGURE 1. TNM staging system applied to carcinoma of the breast.

a. T-1 N-O M-O.

b. T-2 N-1 M-O. Stippling indicates that skin is tethered; axillary nodes are palpable but movable.

c. T-3 N-2 M-O. Crosshatching indicates complete fixation; small areas of ulceration and skin nodules are perceptible and axillary nodes are matted.

d. T-3 N-O M-1. Stippling indicates chest-wall invasion.

(Reproduced with permission from: Harmer, M.: The staging of cancer. In Raven, R. W.: Cancer. London, Butterworth & Co., Ltd., 1958, vol. 4, p. 6.)

which the patient can be examined and the possible presence of infection in the primary growth.

If the malignant process has been extended through the blood stream or lymphatic system beyond the region of immediate lymphatic drainage, the symbol M-1 is used. M-O indicates that no distant metastasis is detectable.

The 1958 proposal of the Research Commission, International Union Against Cancer,[3] contained the recommendation that the symbol M be used if there was evidence of distant metastasis and that it be omitted if no such evidence existed. Two task force subcommittees (breast and larynx) of the American Joint Committee for Cancer Staging and End Results Reporting[4] favored a choice between the classifications M-O and M-1 for the benefit of the statistician, and urged inclusion of the symbol M in all descriptions. The Joint Committee approved this change; thus it is included in the present article. Specialized examination procedures such as roentgenography may be needed to elicit this information.

The TNM system thus represents a gradation of degree in extension of the tumor. A neoplasm with no evidence of regional lymph node disease or of distant metastasis would be recorded as T-1 N-O M-O. An advanced lesion with fixed regional lymph nodes and

TABLE 1

APPLICATION OF TNM STAGING SYSTEM TO BODY SITE X

STAGE	
1	T-1 N-O M-O; T-2 N-O M-O
2	T-1 N-1 M-O; T-2 N-1 M-O
3	T-3 N-O M-O; T-3 N-1 M-O; T-3 N-2 M-O T-1 N-2 M-O; T-2 N-2 M-O
4	Any stage with M-1

pulmonary metastases might be indicated by T-1 N-2 M-1. From the many possible combinations of symbols, four stages can usually be derived for a particular site, according to the known prognosis of disease. The symbols of the system are, in fact, easier to understand when used in this way. An example applied to a theoretical situation is shown in table 1.

Present Status of the System

The Research Commission of the International Union Against Cancer submitted its proposal on the TNM staging system for study in the latter part of 1958. Within a few months the American Joint Committee for Cancer Staging and End Results Reporting had appointed task force subcommittees to review staging systems for malignant tumors of the breast and larynx, the first two sites for which the TNM system was adapted. The Joint Committee, headed by Dr. Copeland and composed as described previously, also designated a task force subcommittee on lymphoma and related diseases.

TABLE 2

TNM STAGING SYSTEM FOR CARCINOMA OF THE BREAST (TENTATIVE)[4]

STAGE	
1	T-1 N-O M-O; T-2 N-O M-O
2	T-1 N-1 M-O; T-2 N-1 M-O (Includes all N-1 M-O except for T-3)
3	T-3 N-O M-O; T-3 N-1 M-O; T-3 N-2 M-O (Includes any combination with either T-3 or N-2 with M-O); T-1 N-2 M-O; T-2 N-2 M-O
4	Any stage with M-1

Definite progress has been made in most of these projects. At the June 1, 1959, meeting of the Joint Committee, reports of the task force subcommittees on breast and larynx were revised and approved.[4] They were circulated among members for final consideration at the Joint Committee's annual meeting on January 8, 1960. As an example of specific application of the TNM formula, the tentative staging for breast cancer is shown in table 2. Definitions of T, N and M are given in table 3.

TABLE 3

DEFINITIONS IN TNM STAGING SYSTEM OF CARCINOMA OF THE BREAST (TENTATIVE)[5]

T	N	M
1 Tumor of 2 cm. or less in its greatest dimension Skin not involved Or Paget's disease	O No clinically palpable axillary lymph node metastasis	O No distant metastasis
2 Tumor larger than 2 cm. Or skin attachment (dimpling of skin) or nipple retraction (in subareolar tumors) No pectoral muscle or chest wall attachment	1 Axillary lymph node(s) metastasis clinically palpable but freely movable 2 Homolateral axillary or infraclavicular node(s) clinically palpable, fixed to one another or to other structures	1 Clinical and radiographic evidence of metastasis except those to axillary or infraclavicular lymph nodes
3 Tumor of any size with any of the following: skin infiltration, ulceration, peau d'orange, skin edema, pectoral muscle or chest wall attachment		

Task force subcommittees recognized that in individual studies additional information based on histologic study of operative specimens is desirable. Nevertheless, the recommendation was made that such data be included in the form of an addendum, prefaced by the letter P. Thus, original classification remains the same but a final clinical staging, based on microscopic study, is available. It must also be realized that assignment of cases to advanced categories on a clinical basis only, which are later found to belong in the early category, will enhance the survival rate of advanced cases. If this number is large, it will partially invalidate reports of results.

A preliminary report of the subcommittee on lymphoma indicated an exception to the trend of progress in adaptation of the staging system. The TNM formula, committee members found, could not be readily adapted to systemic forms of these diseases. Further study is planned, however, to try to devise a workable system of staging within this category.

Task force subcommittees were most recently appointed to study adaptation of the TNM method to staging of tumors of the bladder and cervix. American workers hope by 1962 to be able to present a proposal for world-wide staging in all sites classifiable by the system.

As reports of the various task force subcommittees are approved in final form, they will be submitted to the sponsoring organizations of the Joint Committee for Cancer Staging and End Results Reporting for review and approval. Brochures that contain one or more reports will then be printed for distribution.

Staging and the Individual Physician

In an analytic study of the results of one of the first intensive statewide programs to reduce the delay between first symptom and treatment of cancer, it was found that the pivotal figure in the reduction of the delay was the family physician.[5] While seven years of intensive educational effort had not reduced the time people waited until they went to a physician, the physician had cut in half the time elapsing from the first visit to treatment.

The practicing physician can be counted on to accommodate to situations that will improve the outlook for his cancer patients. When he familiarizes himself with the TNM method for the staging of cancer, uses the classifications established for specific anatomic sites as they are released, and reports his data, either separately or in collaboration with members of his county or state medical society, he will make possible a comparison of his results with others, thereby helping to determine the norm.

It is not inconceivable that by pooling results on this part of the cancer problem, an index of improvement in the norm may be created that will be sensitive to even minor fluctuations. Steady improvement of basic history taking and record keeping is obvious wherever a cancer record registry operation is in existence. Such operations are increasing. The terminology of the present staging manuals is forthright and easily followed. It is planned for adaptation to mechanical handling. Service bureaus under close supervision of informed physicians or their agents are set up to process the cards and produce the tables of results.

In conclusion, the approach to complete usage of the multithousands of records of experience in individual cancer cases is at hand. Since adequately kept and reported data are the substance sought, staging is the key. Analysis, rapid dissemination of each new item promising improvement, and application of such knowledge could conceivably raise the entire level of current experience to the theoretical height of cure for one-half the patients with cancer.

REFERENCES

1. Macdonald, E. J.: Criteria for reporting end results. Am. J. Roentgenol. 60:832 (December) 1948.
2. U.S.A. National Committee, International Union Against Cancer: The international union against cancer. J. Nat. Cancer Inst. 13:283 (October) 1952.
3. Research Commission, International Union Against Cancer: Clinical stage classification and presentation of results; malignant tumours of the breast and larynx, 1958 Proposal, Paris.
4. Joint Committee for Cancer Staging and End Results Reporting, June 1, 1959, meeting, Boston. Unpublished data.
5. Macdonald, E. J. and Frances, A.: Evaluation of cancer control methodology. Am. J. Pub. Health 30:483 (May) 1940.

Treatment of Early Cancer of the Breast

JEROME A. URBAN*

Memorial Center for Cancer and Allied Diseases, New York

JEROME A. URBAN

At present the definitive treatment of primary breast cancer consists of a local attack on the primary tumor and its regional lymph node metastases by radical surgery and x-ray therapy. Success is possible only when the cancer is confined to the breast and its regional node depots in the absence of established systemic spread. This favorable setup is most likely to be present when the breast cancer is detected early in its clinical course. In order to increase the salvage of cases of primary breast cancer it is essential to combine early diagnosis with adequate therapy.

It is not sufficient to bring the patient to therapy after the cancer has developed its pathognomonic signs such as skin dimpling, nipple retraction, enlarged axillary nodes, etc. Every effort must be made to detect the lesion before these typical late signs become evident. Public education regarding the importance of early diagnosis of cancer and, in particular, the advocacy of self-examination of the breasts are yielding a greater number of patients with minimal clinical signs. It is difficult to detect these lesions, but since the results of therapy of breast cancer are directly proportional to the extent of disease present at the time of treatment, every effort must be made to detect these lesions as early as possible (table 1).[1]

Routine excision of persistent, dominant nodules in the breast with immediate frozen-section pathologic examination is a well-established procedure. Its liberal application is resulting in the detection of increasing numbers of early breast cancers. During the last decade several other methods have been developed in an effort to detect early breast cancer. Roentgenographic examination of the breast has attained widespread practice in France and has been developed in this country particularly by Gershon Cohen and his associates in Philadelphia. The accuracy of this method ranges from approximately 50 to 90 per cent, depending on the setting. Some clinically unexpected breast cancers have been detected in this manner. The general adoption of routine roentgenographic examinations of the breasts has not yet met with widespread acceptance.

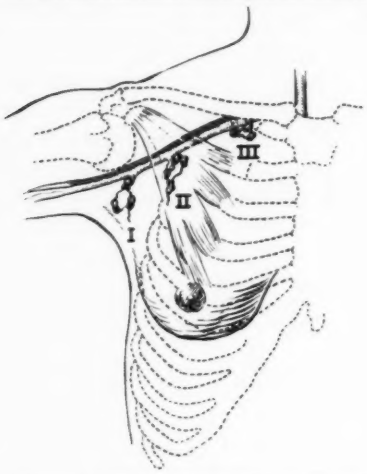
Cytologic examination of nipple secretions

*Assistant Attending Surgeon, Memorial Center for Cancer and Allied Diseases, New York, New York.

TABLE 1

PRIMARY OPERABLE BREAST CANCER

730 Patients Treated by Radical Mastectomy and Postoperative X-ray Therapy (Memorial Hospital, 1945)



NODE INVOLVEMENT IN AXILLA	FIVE YEAR SURVIVAL RATE (PER CENT)
Negative	83.2
Positive	
Level I	65.2
Level II	44.9
Level III	28.4
Over-all group	54.4

The extent of disease at the time of operation is the most important factor governing the prognosis. As the higher levels of the axillary nodes become involved, the five year salvage rate drops for patients who had adequate therapy. Figures taken from Adair.[1]

comprises another attack. Occasional unsuspected breast carcinomas are found by this method, but on the whole its practicability is limited by the small take obtained from extensive clinical and laboratory effort. Of 1600 patients recently examined at Memorial Center and New York Hospital and reported by Papanicolaou and associates, only 900 patients showed any nipple secretions. In the asymptomatic patients the incidence of nipple secretion fell to the level of about 20 per cent, being slightly higher in the premenopausal group. Two carcinomas were picked up in patients with negative clinical findings in this group of 900 examinations. Both of these intraductal lesions were treated by radical mastectomy and the patients are free of disease to date. The limitations of this approach are evident since most breast cancers show no nipple discharge. Nevertheless, this is a useful tool in the proper setting.

Infrared photography has been used to detect dilated blood vessels which, in turn, are often related to the presence of malignant disease of the breast. However, this is a gross procedure and probably will not be effective in detecting early cancers. More recently thermography—scanning the breast and comparing temperature readings over tumors with readings over surrounding normal breast tissue—has been described.

A liberal policy of excising persistent masses of the breast has disclosed a goodly number of clinically unsuspected breast cancers before they have developed the pathognomonic signs of breast cancer and while most of these lesions were comparatively localized in extent. At the Memorial Center, between 1945 and 1948,[2] 1,434 local excisions were performed on clinic cases for clinically benign or indefinite breast lesions (figure 1). Frozen-section examinations of the operative specimens revealed 154 cancers (10 per cent) at the time of surgery. Comparison of these cases with a group of clinically diagnosable breast cancers undergoing therapy during the same period revealed an improved salvage rate as well as a higher proportion of patients with more localized disease in the clinically indefinite group.

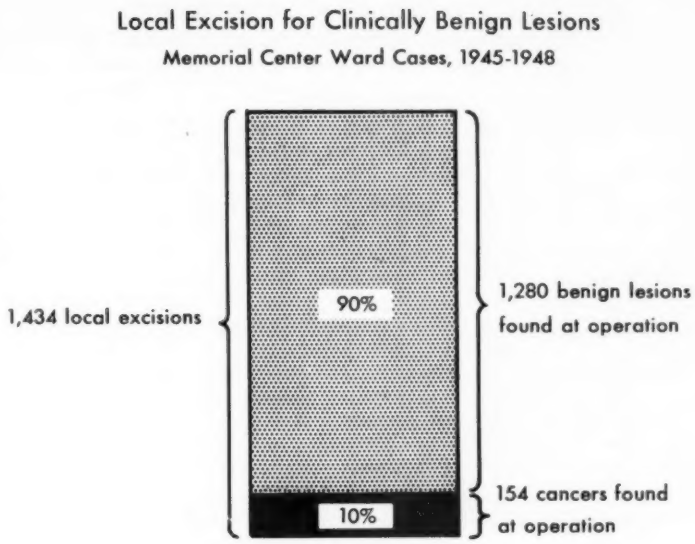


FIGURE 1. Approximately 10 per cent of clinically indefinite lesions will prove to be carcinoma following local excision with frozen-section examination.

A recent study of 200 consecutive private cases of breast cancer treated by radical surgery and x-ray therapy revealed that the average lesion in the clinically indefinite material measured 2 cm. in diameter, whereas in the clinically diagnosable group the average diameter was 2.5 cm. (tables 2, 3 and 4). The distribution of various types of histology and grading was found to be almost identical in the two groups.

Analysis of 1000 cases of primary operable breast cancer treated by radical mastectomy and postoperative x-ray therapy at the Memorial Hospital showed that 78.9 per cent were clinically diagnosed as carcinoma preoperatively (table 5). In the remaining 21.1 per cent a clinical diagnosis of either a benign nature or an indefinite lesion was made. In the clinically apparent group only 52 per cent survived five years and 45 per cent were free of disease at five years. However, in the early group in whom the typical clinical signs of breast cancer had not yet developed at the time of treatment, 74 per cent survived five years and 69.2 per cent were free of disease at five years. This improvement is quite understandable when one compares the extent of disease in the two groups. In the clinically apparent material only 32 per cent showed a negative axilla, whereas in the earlier clinical material 60 per cent showed a negative axilla. Furthermore, we find a higher proportion of patients with limited axillary node involvement in the earlier material.

The general improvement in the treatment of primary operable breast cancer in the large centers in this country is due to the fact that we are now treating a higher proportion of patients whose axillary nodes are clear or who have limited involvement of the axillary nodes. The preceding statistics refer to *infiltrating* breast cancer.

It is only through the fortuitous finding of noninfiltrating cancer by surgical removal of a thickening of the breast that we can detect the really early lesions, the so-called pathologists' cancers. It is unfortunate that we do not have a more definite means of detecting these lesions during this stage. More than 90 per cent of patients with noninfiltrating breast cancer found at the time of local excision, who were then treated by radical mastectomy, survived free of disease at five years. Of 50 cases surveyed, 14 per cent of patients showed extension beyond the breast; in five instances, positive nodes were found in the axilla, and two other patients died of metastatic disease (table 6). In 50 per cent, residual tumor was

TABLE 2

FIVE YEAR SALVAGE RATE OF 200 CONSECUTIVE CASES OF PRIMARY OPERABLE BREAST CANCER*

	TOTAL CASES		FIVE YEAR SURVIVAL		NO EVIDENCE OF DISEASE AFTER FIVE YEARS	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Over-all group	200	100.0	132	66.0	116	58.0
Axilla —	91	45.5	76	83.5	71	78.0
Axilla +	109	54.5	56	51.4	45	41.0
Cancer diagnosed clinically	143	71.5	90	63.0	76	53.0
Axilla —	55	38.5	45	82.0	42	76.0
Axilla +	88	61.5	45	51.0	34	38.6
Cancer not diagnosed clinically	57	28.5	42	73.0	40	70.0
Axilla —	36	63.0	31	86.0	29	80.0
Axilla +	21	37.0	11	52.0	11	52.0

*Includes three lost to follow-up and considered dead.
Data taken from private patients (1949-1953) who were treated by radical surgery and postoperative x-ray therapy. Note the correlation between the high incidence of patients with negative axillae and the high salvage rates.

TABLE 3

DISTRIBUTION OF METASTATIC AXILLARY NODES

INVOLVEMENT	OVER-ALL GROUP		CANCER DIAGNOSED		CANCER NOT DIAGNOSED	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Axilla +	109	54.5	88	61.5	21	36.8
Level I	32	29.0	24	27.0	8	38.0
Level II	28	25.0	25	28.0	3	14.0
Level III	49	45.0	39	44.0	10	48.0

Extent of axillary node involvement in 200 private patients with primary breast cancer, showing higher incidence of lower level of axillary involvement in the early material.

TABLE 4

FIVE YEAR SURVIVAL RATES FOR PATIENTS WITH NO CLINICAL EVIDENCE OF DISEASE

NODE INVOLVEMENT IN AXILLA	OVER-ALL (PER CENT)	CANCER DIAGNOSED (PER CENT)	CANCER NOT DIAGNOSED (PER CENT)
Negative	78.0	76.0	80.0
Positive			
Level I	65.0	62.5	75.0
Level II	53.5	52.0	66.0
Level III	18.0	15.0	30.0
Over-all group axilla +	41.0	38.6	52.0

Data taken from private patients (1949-1953) who were treated by radical surgery and x-ray therapy. Salvage rate is inversely proportional to the extent of axillary node involvement.

found at the final operation. Ozzello[3] has demonstrated basement membrane defects in most cases; others believe that minimal areas of infiltration are not detected. Intraductal carcinoma in which infiltration is not seen is a dangerous lesion and should be treated by radical mastectomy.

The chance finding of *in situ* lobular carcinoma in a locally excised specimen should be followed by more complete surgery. When *in*

TABLE 5

SURVIVAL RATES OF 1000 PATIENTS WITH PRIMARY OPERABLE BREAST CANCER

	TOTAL CASES		FIVE YEAR SURVIVAL		NO EVIDENCE OF DISEASE AFTER FIVE YEARS	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Over all group	1000	100.0	567	57.0	500	50.0
Axilla —	375	37.5	303	80.8		
Axilla +	625	62.5	264	42.0		
Cancer diagnosed clinically	789	78.9	411	52.0	354	44.8
Axilla —	250	32.0	196	78.4		
Axilla +	539	68.0	215	40.0		
Cancer not diagnosed clinically	211	21.1	156	74.0	146	69.2
Axilla —	125	59.2	107	85.6		
Axilla +	86	40.8	49	57.0		
Not included						
Local excision elsewhere	17		8	47.0		
Lost to follow-up	11					
Noninfiltrating cancer	7		7	100.0	7	100.0

Data taken from 800 patients at Memorial Hospital between 1945 and 1948 and from 200 private patients (1949-1953) who were treated by radical mastectomy and postoperative x-ray therapy.

TABLE 6

INTRADUCTAL NONINFILTRATING CARCINOMA IN 50 PATIENTS

	PER CENT OF PATIENTS
Findings	
Mass in breast	75
Nipple discharge	30
Extension beyond breast	14
Residual tumor at final operation	50
Positive nodes	10
Results of radical mastectomy	
Five year survival rate	>90
Death from metastases	4

Figures taken from Ozzello[3] and Lucas.[4]

situ lobular carcinoma is inadequately treated by only a local excision, an infiltrating breast carcinoma will develop in approximately 35 per cent of the patients after a lapse of seven years. We believe that this lesion can be controlled completely by simple mastectomy with low axillary dissection.

A generous policy of operating on doubtful or clinically benign lesions of the breast will improve the cure rate of breast cancer, mainly by affording better material in which the cancer is more likely to be confined to the breast and its regional lymph node depots in the absence of established systemic spread. The more complete surgical procedures and the more adequate roentgen-therapeutic methods should be applied mainly to these early cases, because success is possible only when the cancer is confined to the area of treatment in the absence of established systemic metastases. While awaiting the development of more effective means of routine screening for breast cancer, we must depend on excisional biopsy of any persistent, dominant mass in the breast to detect the early lesions. A significant number of clinically apparently benign lesions will prove to be early cancers. These same lesions have a better prognosis after adequate treatment than the average clinically apparent breast cancer. Even if one is not in doubt, a persistent mass in the breast is best removed.

REFERENCES

1. ADAIR, F. E.: Surgical problems involved in breast cancer. (Moynihan lecture.) Ann. Roy. Coll. Surgeons England 4:360-380, 1949.
2. URBAN, J. A.: Early diagnosis of breast cancer. Cancer 9:1173-1176 (November-December) 1956.
3. OZZELLO, L.: The behavior of basement membranes in intraductal carcinoma of the breast. Am. J. Path. 35:887-900 (July-August) 1959.
4. LUCAS, J. C.: Personal communication to the author.

Early Cancer of the Larynx

EDGAR L. FRAZELL AND FRANK R. GEROLD*

Memorial Center for Cancer and Allied Diseases, New York

EDGAR L. FRAZELL

CANCER may arise at any point on the mucous membrane of the intrinsic larynx, the extrinsic larynx, or in the ill-defined region sometimes referred to as the laryngopharynx. Lesions that arise on the vocal cords characteristically produce symptoms of intermittent or persistent hoarseness early in their clinical course, while those arising at other sites are relatively asymptomatic and silent until the growth has attained considerable bulk. Only under exceptional circumstances are these latter lesions diagnosed early. For all practical purposes, therefore, this discussion is, by definition, confined to the treatment of early cancer of the vocal cords.

Criteria for designating a given tumor of the vocal cords as *early* may vary from clinic to clinic, but at the head and neck service of the Memorial Hospital they are essentially the same as the indications for considering treatment by partial laryngectomy. Briefly, such cancers are those confined to one vocal cord only, or those with limited involvement of the anterior commissure and opposite cord. Generally speaking, such lesions are also the ones that are considered favorable for irradiation therapy. Those causing complete fixation of one side of the larynx, those with subglottic extension, and those with more than minimal invasion of the ventricle can hardly be classed as early, and they are unfavorable for treatment by partial laryngectomy or irradiation.

Nature of Our Material

During an 11 year period (1943 to 1953, inclusive), cancer of the intrinsic larynx was diagnosed in 683 patients observed on the head and neck service of the Memorial Hospital (table 1). Unfortunately, in slightly less than one-third of these, 219 patients, were the cancers considered early or favorable for conservative therapy. In line with service policy, partial laryngectomy was advised in 217 patients and irradiation was advised in only two. This report, then, is a résumé of our experience in the treatment of early cancer of the intrinsic larynx by partial laryngectomy. It is outside the scope of this presentation to dis-

*Head and Neck Service, Memorial Center for Cancer and Allied Diseases, New York, New York.

TABLE 1

CANCER OF THE INTRINSIC LARYNX
1943 to 1953, Inclusive

Total patients observed		683
Early or favorable cases		219
Partial laryngectomy advised		217
Partial laryngectomy done	194	
Treatment refused	22	
Preoperative death	1	
Irradiation advised		2

cuss the relative merits of this method of treatment versus irradiation.

Not all patients for whom partial laryngectomy was advised were treated by us. Twenty-two of them failed to return and went elsewhere for advice. Efforts to learn their fate were not uniformly successful, but it is known that most of them were ultimately treated either by partial laryngectomy or by irradiation. One of them returned to us after several years' delay and was salvaged by total laryngectomy. One patient died in the hospital preoperatively of a heart attack. These patients are mentioned only to exclude them from further consideration, since they do not contribute to our assessment of partial laryngectomy as a curative procedure.

This report is based on 194 patients on whom partial laryngectomy was performed by surgeons of the head and neck service during an 11 year period. It represents total experience with this operation only, although inclusion of the two patients treated by irradiation would not alter the results. One of them was cured; the other died of cancer of the stomach within two years after treatment of his vocal cord cancer.

General data—This series of patients with cancer of the vocal cords does not differ particularly from those observed by others. They were predominantly male (table 2)—almost 93 per cent. The age distribution was wide, since the youngest patient was a 26 year old woman and the oldest was an 89 year old man. Both were cured. The majority, of course, were in their sixth and seventh decades. The fact that the majority of these patients were economically privileged may have some significance if the reverse is found to be true for all cancers of the larynx, i.e., both early and advanced. Not many patients exhibiting definite fixation of one side of the larynx were subjected to partial laryngectomy. We feel reasonably sure that where the chart contained no statement regarding cord palsy, there was no fixation. It is of interest that the majority of the lesions were truly infiltrative cancers. The material does not appear to be weighted in favor of the *in situ* group. There were a few instances where the entire lesion seemed to have been removed by biopsy, because the operative specimen failed to show residual cancer. Since serial sections were not done, however, this is a debatable point.

Few surgeons would consider the possibility of performing partial laryngectomy after previous irradiation failure. Yet this was done in two patients in this series and it was successful in one. Serious complications were relatively few in this group of patients. Subcutaneous emphysema of some degree is generally expected, but in one-fourth of the patients it was of sufficient degree to warrant a note on the patient's chart. Bleeding, serious

TABLE 2

CANCER OF THE INTRINSIC LARYNX
INCIDENTAL DATA IN EARLY OR FAVORABLE CASES

Sex	
Men	181
Women	13
Age*	
Youngest	26 yr.
Oldest	89 yr.
Status	
Private patients	117
Ward patients	77
Cord palsy	
Present	15
Not present	117
Not stated	62
Pathologic findings	
In situ cancer	28
Superficial invasive cancer	44
Infiltrative cancer	122
Pretreatment failures (irradiation)	2
Surgical complications	
Emphysema	50
Hemorrhage	5
Postoperative death	1

*Majority in their sixth and seventh decades.

TABLE 3

EARLY CANCER OF THE LARYNX
MULTIPLE PRIMARY CANCERS

27 patients had 30 other cancers:

Lung	6	Floor of mouth	1
Stomach	4	Esophagus	1
Colon	4	Breast	1
Prostate	2	Brain	1
Extrinsic larynx	2	Lip	1
Tonsil	3	Myeloma	1
Thyroid	1	Pancreas	1
		Bladder	1

17 patients died from these secondary cancers within less than one year to 12 years following partial laryngectomy. Four patients probably had secondary vocal cord cancers.

enough to require opening the wound, was recorded in five patients. The one operative mortality was thought to be due to a coronary occlusion rather than to technical difficulties. This record is outstanding in our experience.

Multiple Cancers

It is of interest that in 27 patients in this series cancer developed at other anatomic sites during the period of observation (table 3). This should concern those interested in cancer detection clinics. When one considers the population at risk, the results of cancer detection examinations might be more impressive if these services were extended to include at least all patients who have been cured of cancer. One might even consider limiting cancer detection examinations to this group alone.

TABLE 4

CANCER OF THE INTRINSIC LARYNX
CLINICAL COURSE AFTER PARTIAL LARYNGECTOMY

Patients treated by partial laryngectomy		194 (100%)
Living without disease 5 years after admission		161 (83%)
After initial surgery	145 (75%)	
After secondary treatment*	16 (8%)	
Dead of cancer of the larynx		10
Dead of other causes†		16
Dead (postoperative)		1
Lost		1
Living (cancer of larynx present)		5

*Irradiation 1; secondary laryngofissure 4; radical surgery 11.

†Other cancers 6; coronary occlusion 4; cardiovascular accident 3; pneumonia 1; accidental death 1; obstructive jaundice 1.

Clinical Course After Partial Laryngectomy

As previously stated, 194 patients were treated initially by partial laryngectomy. Five years later, 161—or 83 per cent—of them were living and free from cancer of the larynx (table 4). As will be shown, this is not a true measure of the curability of early laryngeal cancer, nor is it a true assessment of partial laryngectomy as a curative measure when it is employed initially. Although 145 of the 161 patients surviving five years (roughly 90 per cent) were cured on the first "go-round," so to speak, this was only 75 per cent of the total number of patients subjected to partial

TABLE 5

CANCER OF THE INTRINSIC LARYNX
FAILURES OF INITIAL SURGERY

Patients treated by partial laryngectomy		194 (100%)
Initial treatment failed*		32 (16.5%)
Cured by secondary treatment	16	
Dead of disease	10	
Living with disease	5	
Died postoperatively	1	
Initial treatment successful		145 (74.7%)
Dead of other causes†		16 (8.3%)
Lost†		1 (0.5%)

*Treated secondarily by surgery 27; by irradiation 3; not treated 2.

†No evident disease.

TABLE 6

CANCER OF THE INTRINSIC LARYNX
SECONDARY TREATMENT AFTER PARTIAL LARYNGECTOMY FAILED

Total failures of partial laryngectomy		32
Patients treated secondarily*		30
Repeat laryngofissure		5
Cures	4	
Failures	1	
Radical surgery†		22
Cures	11	
Failures	11	

*Postoperative death 1; untreated 1.

†Total laryngectomy, 19 patients; neck dissection, 11 times.

TABLE 7

CANCER OF THE INTRINSIC LARYNX
FIVE YEAR END RESULTS OF TREATMENT BY
PARTIAL LARYNGECTOMY

Partial laryngectomies performed		194
Indeterminate results		17
Dead—other causes*	16	
Lost*	1	
Determinate results		177
Failures		16
Dead (cancer of the larynx)	10	
Dead (postoperative)	1	
Living (cancer present)	5	
Success (living and free of cancer)		161
Cure rates		
Based on partial laryngectomies done 161/194		83%
Based on determinate cases 161/177		90%

*No evident disease.

laryngectomy. An additional 16 patients became five year survivors only after secondary treatment, which included irradiation in one, secondary laryngofissure in four, and total laryngectomy or neck dissection or both in 11.

One might gain an unduly pessimistic view of the efficiency of partial laryngectomy or of the choice of patients selected for it, unless it is pointed out that only 10 patients died of cancer of the larynx, five were living with the disease at five years, and there was one operative mortality. The number of undisputed failures, 16 patients, is the same as the number of patients in whom the results of treatment were indeterminate because of death from other causes before five years, but after apparently successful treatment. The same data are presented in table 5 which emphasizes the fact that although partial laryngectomy failed initially in 32 patients, one-half of them were ultimately salvaged by other measures.

A brief résumé of the secondary treatment methods employed is of interest (table 6). We suspect, and there is considerable clinical and laboratory evidence to support it, that when laryngofissure was performed secondarily, the cancer was a new one and not a recurrence. It is also possible that some of the patients subjected to total laryngectomy could have been treated in this manner. One out of the three patients secondarily treated by irradiation was cured.

End Results of Treatment

End results, as measured by freedom from disease five years after treatment by partial laryngectomy, may be calculated (table 7). All patients treated by this method are accounted for. Those whose results were indeterminate are indicated. It is noteworthy that only one treated patient was lost to follow-up. This is unusual in our experience. The cure rate based on total operations done was 83 per cent. When the more rational method is employed of basing the rate on the cases in which results are determinate, the cure rate is 90 per cent.

Treatment of Early Cancer of the Cervix

HOWARD ULFELDER*

Harvard Medical School, Boston

Definition

HOWARD ULFELDER

EARLY cancer of the cervix includes carcinoma *in situ*, carcinoma *in situ* with microscopic invasion, and invasive carcinoma stage I (International Clinical Classification). Histologically, these lesions are epidermoid cancers, except for about 5 per cent adenocarcinomas, but neither the staging nor the treatment is modified if adenocarcinoma is found.

The first step in the management of these conditions is to define the geographical extent of disease, in both area and depth. Careful inspection and palpation must be done with the patient under anesthesia, using aqueous iodine solution (Schiller's test) to help differentiate between normal and abnormal epithelium. Biopsic specimens are taken from all suspicious areas and are labeled, and blind biopsies are done with a small curet to obtain specimens from the endocervical canal and from the lower surface of the endometrial cavity. If carcinoma *in situ* has been described in previous biopsies, it is vital that we know whether invasion anywhere has occurred. In this situation a cone biopsy of the entire external cervical os is desirable,[1] using no cautery or diathermy until after excision of the specimen.

X-ray examination of the urinary tract and of the lungs and skeleton, cystoscopy and proctoscopy, and similar studies will rarely show abnormality in the early cases. Often, however, they will be helpful later and will aid in the re-evaluation of pelvic findings, particularly in cases where there is doubt about cure.

When all the data are available, the case is classified in one of the three categories previously listed.

Treatment

Carcinoma *in situ* can be assumed not to extend deeper than the epithelial basement membrane. Adequate treatment is total removal or total destruction. Hysterectomy which in-

*Clinical Professor of Gynecology, Harvard Medical School; Chief of Staff, Vincent Memorial Hospital; Gynecological Service of the Massachusetts General Hospital, Boston, Massachusetts.

cludes all of the cervix and a fully circumferential cuff of vagina guarantees total removal, particularly if the Schiller test is used to ensure that all nonstaining areas of cervix and vagina have been included in the specimen. In those cases where it is desired to preserve fertility, local excision, conization and cauterization may be used to achieve total removal or destruction, but they are obviously much less certain to accomplish this goal. Repeated careful examinations, Papanicolaou tests and biopsies must be normal before it can be assumed that it is safe to let the patient conceive.

When the patient is pregnant, changes in the cervical epithelium may be histologically indistinguishable from carcinoma *in situ*. Careful endocervical curettage and cold-knife cone biopsies must be done to exclude invasive cancer, but then one can delay further treatment until the patient has delivered. This plan uses our knowledge about the natural history of cervical cancer and, in particular, the known fact that the disease progresses in slow and orderly fashion through its early stages. It must be emphasized that once invasion has been excluded by adequate biopsy studies, there is never a need for haste in applying definitive therapy. If the malignant potential is truly in doubt, either because the patient is pregnant or because the pathologist finds inadequate evidence in the tissue studies, it is always wiser to wait and repeat the examinations after an interval of several months.

There appears to be no increased danger of miscarriage from the manipulation of the cervix necessary in this program of management. A final careful survey to exclude invasion must be done during the last month of pregnancy, and the patient is then delivered as though the cervix were normal. The postpartum follow-up must be strictly maintained until healing of the cervix is complete and both cytologic and histologic studies are unequivocably normal or show persistent cancer *in situ*. Treatment then follows on the basis of clear-cut indications.

Radiation treatment can totally destroy the epithelium of the cervix and upper vagina, but only if the dose delivered to these surfaces is not less than the usual cancericidal one. This requires careful selection and application of radiation sources, with inevitable exposure of bladder, ovaries and other adjacent viscera. Taking all factors into consideration, radiation treatment for carcinoma *in situ* can be justified only in the occasional patient where even hysterectomy carries a prohibitive risk.

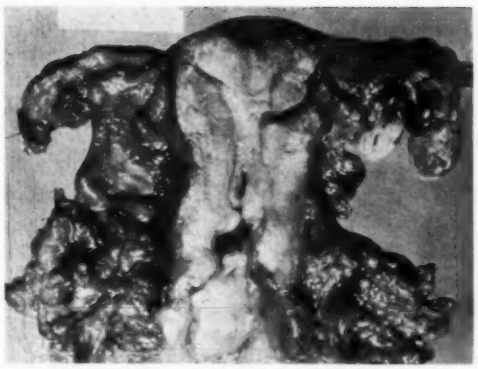


FIGURE 1. Specimen resected for treatment of stage I carcinoma of the cervix. Note en bloc removal of lateral tissues of cervix and upper vagina.

Carcinoma *in situ*, adequately diagnosed and adequately treated, should always be cured. The reported world experience[2] confirms this, so much so that the editors of these reports are recommending omission of stage O in future publications. The sporadic case reports of individuals treated for carcinoma *in situ* with subsequent recurrence of *in situ* or invasive disease always deal with situations where the original diagnosis was not made until after the uterus was removed, or where histologic study of the original specimen was, in retrospect, inadequate to exclude invasive areas already present in the lesion.

Carcinoma *in situ* with microscopic invasion and overt invasive cancer, stage I, are the same disease as far as treatment is concerned. The highest cure rate is reported by those clinics where therapy is guided by the en bloc principle, that is, where the initial assumption is made that cancer may already be present in the cervix, uterus or upper vagina, and in the lateral supporting structures as far as the internal iliac vessels and pelvic

lymph nodes. Whether surgery or radiation is used, it must encompass this volume of tissue. Treatment according to this concept is seldom a simple and never a casual affair. The surgical method requires an operation which is essentially a dissection of the pelvic walls and floor, with preservation of the bladder, ureters and bowel. The uterus, cervix and vagina do constitute the central portion of the removed specimen, but here the resemblance to an ordinary hysterectomy ceases (figure 1).

Adequate radiation cannot be delivered to this same block of tissue by any technic of local application alone. The infinite variety of those in use expresses chiefly man's ingenuity in the effort to give adequate exposure to the uterus, cervix and adjacent areas with minimum risk of damaging the bladder and rectum. No one apparatus or method can honestly be said to be superior to all others. When one considers the variation from case to case in tumor size and shape, depth and course of uterine canal, and length and diameter of vagina, it is at once apparent that one's method must be very adaptable or that several technics must be available to the therapist. Even under ideal circumstances, however, only the central portion of the volume to be treated can be reached, and the peripheral dose must be augmented with radiation from external sources in order to conform with the en bloc principle.

A special situation arises when microinvasion is first seen by the histologist in the hysterectomy specimen removed for carcinoma *in situ*. Here it is no longer possible to apply adequate radiation safely, and the risk of reoperation and radical removal of the necessary additional tissues probably exceeds the threat of death from cervical cancer. It must be emphasized that this paragraph has reference only to cases where the pathologist opines that microinvasion has occurred, or probably has occurred, in what is otherwise seen to be clear-cut carcinoma *in situ*. Moreover the entire cervix has been examined and there is no question whether more definite areas of stromal invasion may also exist. Where unquestioned invasive cancer is found, even in small tumors, the case must be classified and treated as stage I cancer, even though it has been suggested that a high rate of cure would follow much less radical treatment.[3]

About 80 per cent of stage I cancers of the cervix are being cured today in the most successful clinics,[2] regardless of the form of treatment used. In the surgical cases, the failures are chiefly in patients where node metastases were present.[4] Although there is no evidence to explain failure in cases where radiation is used, unsuspected extension outside the field of treatment must be a factor here also. In other words, failure to achieve cure in a stage I case usually occurs when it could not be detected that the cancer, in actual fact, was more extensive than stage I. This defect in our clinical method of staging has long been recognized, but it must be accepted until technics are developed which are more accurate than present ones for staging patients before any treatment is applied.

Most of our knowledge about cancer has been gleaned from well-established and advanced cases. Now the technics of detection and diagnosis are delicate enough to bring us the early, even the incipient case, and there is an irresistible urge to do less to these patients. Emphasis on the rate of cure, as in the past, encourages this attitude, because it is gratifyingly high in early cases. It should be recognized, however, that the patient in every early case has the right to expect a cure, and the focus of interest should be on the *rate of failure to cure* whenever such a patient dies as a result of her disease.

REFERENCES

1. Scott, R. B. and Reagan, J. W.: Diagnostic cervical biopsy technique for the study of early cancer. J.A.M.A. 160:343-347 (February 4) 1956.
2. Kottmeier, H. (ed.): Annual Report on the Results of Treatment in Carcinoma of the Uterus. Stockholm, Sweden, Kungl. Boktryckeriet. P. A. Norstedt & Söner, 1957, vol. 11.
3. Friedell, G. H. and Graham, J. B.: Regional lymph node involvement in small carcinoma of the cervix. Surg. Gynec. & Obst. 108:513-517 (May) 1959.
4. Meigs, J. V.: Radical hysterectomy with bilateral dissection of the pelvic lymph nodes. In Meigs, J. V. (ed.): Surgical Treatment of Cancer of the Cervix. New York, Grune & Stratton, Inc., 1954, pp. 137-216.

Early Cancer of the Rectum

NEIL W. SWINTON* AND JOSEPH C. SNOW†

Lahey Clinic, Boston

NEIL W. SWINTON

ANY discussion of the treatment of early cancer of the rectum should begin with an attempt to answer several questions: What is early cancer of the rectum? How does rectal cancer develop? Does the adenomatous polyp with a carcinoma at its tip eventually develop into metastasizing and fatal malignant disease?

This discussion will not review all the theories which have been presented concerning the origin of rectal cancer. Our purpose is to present the policies of our group at the Lahey Clinic on the treatment of the earliest stages of what we regard as malignant disease of the rectum.

A number of small carcinomas arising within nonpolypoid mucous membrane have been reported. Helwig[1] reported two of these lesions in the colon found at necropsy in a series of 1,460 patients. His findings apparently form the basis for the statement by Spratt, Ackerman and Moyer[2] that the incidence of cancer of the large bowel in the population (45 per 100,000) can be accounted for by the development of these lesions from nonpolypoid mucosa.

We agree that in many instances rectal cancer develops from the rectal mucosa without passing through a polypoid phase, but we do not know how frequently this occurs. At the Lahey Clinic, approximately 6000 diagnostic sigmoidoscopic examinations are performed each year. In 5 per cent of these patients (adults), benign mucosal polyps are found. Our total experience with polyps and cancer of the colon and rectum during the years 1945 to 1954 is shown in table 1. We have not seen clinical cancer less than 0.5 cm. in diameter and have only rarely found cancer less than 1 cm. in diameter.

It seems to us that if the majority of cancers of the colon and rectum do not pass through a polypoid phase, we should see many

*Department of Surgery; †Former Fellow in Surgery, Lahey Clinic, Boston, Massachusetts.

TABLE 1

INCIDENCE OF POLYPS AND CARCINOMA OF THE COLON AND RECTUM
1945-1954

PATIENTS TREATED BY LOCAL EXCISION OR FULGURATION	NUMBER OF PATIENTS
Benign mucosal polyp of rectum	1,168
Benign mucosal polyp of colon	226
Carcinoma in benign mucosal polyp of rectum	24
Carcinoma in benign mucosal polyp of colon	18
PATIENTS TREATED BY RESECTION	**NUMBER OF PATIENTS**
Adenocarcinoma of colon and rectum	1,709
Carcinoma in benign mucosal polyp of colon and rectum	93

more small cancers of the rectum, considering the large volume of sigmoidoscopic examinations we perform each year. This may be partially explained by the policy of our group: Whenever small tumors, less than 0.5 cm. in diameter, are found within reach of the 25 cm. sigmoidoscope, the tumors are immediately destroyed by fulguration, without preliminary histologic examination. These patients have always had a careful follow-up study and we have never had reason to regret this policy. Histologic studies are always made on tumors with a definite pedicle when they can be removed in their entirety, and multiple biopsy specimens are always taken when the size of a sessile polyp warrants this procedure. It is entirely possible that we have destroyed small, early cancers of which we have not been aware.

Shields Warren and one of us (N. W. S.)[3] in a review of 827 of our patients in whom resections for cancer had been performed in the eight years preceding 1939, found cancer with persistent polypoid tissue in 14 per cent. Ackerman found no residual polypoid tissue in the 298 specimens of cancer in the series which Spratt, Moyer and he reported.[2]

Possibly the cancer found in many mucosal polyps is coincidental and has always existed as cancer. This theory is similar to the belief many pathologists hold about the relation of the thyroid adenoma to cancer.

Ewing,[4] discussing particularly the papillary or villous type of tumor we believe to be only a growth variant of the adenoma, Dukes,[5] Warren,[3] Helwig[1] and Bacon, Laurens and Peale[6] all agree with our hypothesis that there is an intimate relation between benign mucosal polyps and adenocarcinomas of the colon and rectum and that adenomas of the large bowel are true tumors frequently associated with early cancer and should be destroyed or removed when discovered.

From our clinical experience, however, unquestionably many early cancers of the rectum are slow growing and metastasize late in their development. The growth history of these cancers indicates that many can be managed more conservatively than is possible with other types of cancer. Turnbull,[7] Lochridge and Jackman,[8] and McKay and McMahon[9] have reported similar experiences.

Years ago, Warren[3] presented the histologic criteria for malignancy in a polyp which we still follow: (1) anaplasia, (2) irregularity of architecture, and (3) invasion of the growth beyond the intestinal mucosa. He believed that two of these three abnormalities had to be present for the diagnosis of cancer, with one exception: Lymphatic or intravascular invasion always denoted malignant disease. Our pathologists have continued to follow these criteria in the diagnosis of histologic cancer. In terms of treatment, we are particularly interested in the presence or absence of invasion—invasion of the stalk and base of these tumors and invasion of the adjacent wall of the bowel.

In determining treatment for the patient in whom these histologic criteria of malignancy in a polyp have been established, the importance of the clinical characteristics of these tumors cannot be overemphasized. Fixation, induration—particularly at the base of the larger tumors—and ulceration almost always indicate clinical cancer and the need for radical surgical treatment. A great deal of confusion has existed among surgeons and pathologists about the terminology for many of these borderline tumors and the interpretation of the histologic and clinical findings. Pathologists must be experienced in the interpreta-

TABLE 2

LOCATION OF MALIGNANT POLYPS TREATED CONSERVATIVELY

Rectum and rectosigmoid		24
Inches from anus		
0 to 3	4	
3 to 6	13	
6 to 9	7	
Sigmoid		14
Descending colon		3
Transverse colon		1
TOTAL		42

tion of their findings in determining cancer in polyps, and surgeons and pathologists must cooperate closely in determining the type of treatment for each patient.

Whenever a polyp is diagnosed as histologic cancer, or whenever the surgeon suspects cancer, the policy of our group is to hold a conference on the case in question and to review carefully all phases of the patient's history and the physical and pathologic findings before making a final decision as to treatment.

The surgeon should be experienced in the management of these tumors and familiar with the significance of induration, fixation and ulceration. He must be familiar with the terminology used by his pathologist and appreciate the pathologist's description of the histologic findings. The pathologist must have the opportunity to examine the entire polyp whenever possible, or multiple specimens when necessary. He should never consider a tumor malignant on borderline evidence, and he should be thoroughly experienced in detecting cancer in tumors of the colon and rectum. Our impression is that the frequent failure in cooperation and understanding between surgeon and pathologist has been responsible for much of the confusion that exists on this subject today and perhaps for some of the discrepancies in statistics that have been published.

If actual histologic invasion of blood vessels or lymphatics, stalk or base of the pedicle, or adjacent bowel wall is present in polyps, radical surgical treatment of the cancer should be instituted without delay. We have performed resections of the rectum and had our pathologists report that no residual cancer was found. This has not been disconcerting to us, however, since often it is technically impossible to do the type of serial section that would be necessary to find isolated cancer cells in such removed tissue. Our pathologists believe that we are accurately estimating the tumors that do require radical surgical treatment. In a small number of patients, however, polyps have been found that present the histologic criteria of malignancy but do not reveal invasion of the pedicle, base of the polyp, or adjacent bowel wall, and in our experience these polyps do not require the use of radical surgical procedures.

In preparation for this presentation we reviewed our experience with malignant polyps from 1945 to 1954 (table 1) and found 42 patients with polyps showing early cancer who were treated by local excision or fulguration. No deaths occurred in the group and there have been no recurrences to date. Resections were performed in the remaining 93 patients who had polyps showing malignant changes. The fact that one-third of these patients with polyps showing early cancer have been treated conservatively without further difficulty is significant to us. With further experience and a better understanding of the growth pattern of these tumors, possibly this percentage may be increased. At the present time we would not agree with the position of Spratt, Ackerman and Moyer that the majority of these polyps are innocuous.

A review of the symptomatology in this group of patients revealed nothing significant. Seven patients presented no symptoms referable to the gastrointestinal tract. Twenty-eight, or 47 per cent, were examined because of rectal bleeding, but in the majority this bleeding resulted from anorectal disease, usually hemorrhoids. Nine per cent of these patients had a history of previous colon or rectal polyps or cancer.

In six cases the diagnosis of tumor was made from digital examination alone, and in 68 per cent polyps were seen on sigmoidoscopic examination. The remainder were found on radiologic studies of the colon. Table 2 illustrates the location of these tumors. The

TABLE 3

SIZE OF MALIGNANT POLYPS

CENTIMETERS	NUMBER OF CASES
0.5 to 1.0	6
1.0 to 1.5	9
1.5 to 2.0	12
Larger than 2.0	15
TOTAL	42

tumors varied in size from 0.5 to 5.5 cm. in diameter, as shown in table 3.

Snare excision of the lesions through the sigmoidoscope was performed in 16 cases, surgical excision in two and colotomy in 19. The lesions were biopsied and destroyed by electrofulguration in five cases; these included four adenomatous or villous-type tumors that showed early malignant change histologically. Multiple polyps were found in 34 per cent of the patients.

The type of treatment that may be safely employed for tumors seen through the 25 cm. sigmoidoscope will depend on the experience of the surgeon and the equipment available. For many surgeons who are occasionally confronted with this problem and who have not had extensive experience, the best procedure may be to remove tumors above the peritoneal reflection by colotomy. In our own group, with considerable experience, we remove all tumors visualized with the 25 cm. instrument when the tumor can be seen in its entirety, is freely movable, and when adequate illumination, suction and other essential equipment are available. Snare excision with further fulguration of the base, if necessary, is suitable for most polyps with a definite pedicle. For sessile tumors, when a snare cannot be satisfactorily applied, fulguration is satisfactory after multiple biopsies. For tumors low in the rectum, surgical excision may be desirable. Because of the known tendency of large papillary adenomas or villous-type tumors to recur as a result of peripheral growth, excision is desirable whenever possible. Sometimes this can be done by prolapsing the tumor outside the anal orifice, and many surgeons prefer a posterior proctotomy.

Unfortunately, the majority of the villous tumors are large and are found in the lower rectum. Occasionally, the choice is an abdominoperineal resection or a pull-through type of procedure for complete removal. With these large tumors, our policy is usually to do repeated biopsies, snare removal and fulgurations. We do not believe these tumors are potentially any more malignant than the usual adenoma, although many will show minute foci of histologic cancer on multiple section. In a small number of instances, because of stricture formation after repeated fulgurations over a period of years, we have employed abdominoperineal resections, since we were unable to keep the entire rectum under continuous observation.

When the tumors are above the practical reach of the sigmoidoscope, colotomy is necessary for local excision. If the question of invasion cannot be settled by an immediate frozen-section examination at the time of colotomy, a segmental resection may be indicated. We disagree emphatically with the surgeon who advocates total colectomy for the presence of one or a small number of benign mucosal polyps of the rectum or colon, if these polyps can be removed locally and do not present both clinical and histologic evidence of invasive cancer. We do not believe it justifiable to temporize with the tumor that shows invasive cancer, however, any more than in the case of cancer in any other organ.

A factor to emphasize is that patients with polyps showing early cancer must be carefully and individually selected; their history and the clinical and histologic findings must be scrutinized by both surgeon and pathologist before conservative management is justified. Another essential factor is to observe these patients indefinitely—not only as we would study all patients with clinical metastasizing cancer, but also because we know from experience that in patients who have rectal and colonic cancer or benign mucosal polyps the tendency for the development of subsequent polyps and cancer is greater than in patients who have not had previous tumors. In a five year follow-up study of a series of 500 patients who had benign mucosal polyps, sigmoido-

scopy and air contrast studies showed that either polyps or cancer had developed in 8 per cent.

Summary

Our entire experience over a nine year period with adenocarcinoma of the colon and rectum, benign mucosal polyps, and mucosal polyps showing early histologic malignancy has been presented.

The number of patients with polyps showing early cancer that can be treated conservatively has been a very significant group in our experience, and the condition should be recognized by all surgeons and pathologists.

Although the complete story of the origin of rectal and colonic cancer is not completely understood, our experience demonstrates that there is a most intimate relationship between benign mucosal polyps of the large intestine and cancer. Whether rectal cancer originates in benign mucosal polyps or exists in polyps coincidentally has not been established, but from the standpoint of treatment, polyps when found should be removed or destroyed.

Polyps showing histologic cancer that do not reveal invasion of the stalk or the adjacent bowel wall can be treated conservatively, but when such tumors show definite invasion, radical surgical treatment is indicated.

REFERENCES

1. Helwig, E. B.: The evolution of adenomas of the large intestine and their relation to carcinoma. Surg. Gynec. & Obst. 84:36-49 (January) 1947.
2. Spratt, J. S., Jr., Ackerman, L. V. and Moyer, C. A.: Relationship of polyps of the colon to colonic cancer. Ann. Surg. 148:682-698 (October) 1958.
3. Swinton, N. W. and Warren, S.: Polyps of the colon and rectum and their relation to malignancy. J.A.M.A. 113:1927-1933 (November 25) 1939.
4. Ewing, M. R.: Villous tumours of rectum: Hunterian lecture. Ann. Roy. Coll. Surgeons England 6:413-441 (June) 1950.
5. Dukes, C. E.: Pre-cancerous conditions of the colon and rectum. J. Roy. Coll. Surg. Edinburgh 3:182-192 (March) 1958.
6. Bacon, H. E., Laurens, J. and Peale, A. R.: Histopathology of adenomatous polyps of the colon and rectum. Surgery 29:663-677 (May) 1951.
7. Turnbull, R. B., Jr.: Carcinoma in polyps of the colon and rectum; a study of 86 treated patients. Dis. Colon & Rectum 1:44-48, 1958.
8. Lochridge, E. P. and Jackman, R. J.: Evaluation of conservative management of certain polypoid lesions of the lower part of the large intestine. *Ibid.* 1:101-109 (March-April) 1958.
9. McKay, J. L. and McMahon, W. A.: Management of adenomas of the colon and rectum showing malignant changes: Report of 44 cases treated by local removal. *Ibid.* 2:298-302 (May-June) 1959.

Surgical Treatment of Early Carcinoma of the Face

KENNETH L. PICKRELL, NICHOLAS GEORGIADE, JEROME ADAMSON AND GUIDO MATTON*

Duke University Medical Center, Durham, North Carolina

KENNETH L. PICKRELL

CANCER of the face, because of its accessibility, offers an unparalleled opportunity for early diagnosis and treatment. When a tumor attracts attention early and is readily accessible to observation and treatment, its nature is more likely to be understood than is that of tumors arising in deeply situated organs. From the viewpoint of ease of study, skin tumors are, therefore, in a particularly favorable position. Because of this, a good deal is known about some skin tumors, and the results of early, intensive treatment are quite favorable. However, in spite of the intensive educational crusade against cancer during the past decade, which has made both the public and physicians ever more alert to recognize early cancers, one is still confronted with a relatively large group of patients with active lesions who, in many instances, have been "treated" or "followed" for months or even years.

Too much emphasis cannot be given to the importance of eradicating completely the primary lesion when it is first seen. Inadequate therapy, whether with surgery or irradiation, only results in residual and recurrent disease, which may require an extensive or a destructive operation to effect a cure. Furthermore, residual cancer cells may have a tendency to become increasingly resistant, and oft-repeated procedures may actually accelerate the growth of the tumor. Eller and Eller,[1] Conway,[2] Ward and Hendrick,[3] Martin,[4] McDowell, Brown and Fryer,[5] and others, have repeatedly stressed this point. Blair[6] has stated that it is not so much the lack of treatment or poor selection of the kind of treatment that has handicapped the average recurrent case that we encounter, but the lack of conviction, the use of temporizing methods, or puttering treatment that lowers the quality of our average results.

Cutaneous cancer accounts for from 40 to 60 per cent of all types of malignant lesions seen by the family physician.[7] It is essential, therefore, that the family physician recognize

*Department of Plastic and Maxillofacial Surgery, Duke University Medical Center, Durham, North Carolina.

the wide variation in the behavior of tumors at different times and in different locations. Because of the complex nature of malignant disease, there is no "routine operation" or "routine therapy." And the physician must always remember that he is dealing with a human being as well as a neoplastic process. While the surgeon's role may be that of key member of a team which consists of a radiologist, an oncologist, the family physician, and the patient's family, all must maintain a continued interest in the control of the cancer in a given patient, whether the disease appears to be cured, arrested or to have recurred.

Even though primary tumors of the face and neck are accessible and should lend themselves to early diagnosis and treatment, there is still much to be desired in the control of cancer in these locations. Our medical students of today are our physicians of tomorrow. All physicians, in the course of their daily work, see many skin lesions of the face. Some are dermatologic problems, some are benign lesions, others are important because of potential malignant change. Finally, some lesions may be malignant when first seen or may be metastatic from underlying malignant disease. This paper, therefore, is presented primarily for the student and the family physician rather than for the specialist. There are no statistics. The basic principles in the recognition, the behavior and the surgical treatment of neoplastic lesions of the face are outlined without any adornments whatever. While no one can say just how an individual cancer will respond, there are some general rules which may serve as helpful guides.

Etiology and Predisposing Factors

While it is not known why cancer cells become pathologic or malignant, nevertheless, certain factors are of definite significance. Skin cancers tend to develop more frequently in blond individuals and those with thin, dry skin. Skin carcinomas are encountered infrequently in the yellow races of the Orient, the olive-skinned Italians and South Americans, and are rarely seen in the Negro. However, those individuals (predominantly men) with "Scotch-type" skin (blond hair and beard, blue eyes, thin and dry skin, ruddy cheeks) who, because of their outdoor work and occupations (farmers, ranchers, fishermen, sailors, etc.), are exposed for long periods to intense sunlight, wind and salt air frequently do develop cutaneous carcinomas. This is a distinct clinical entity called "farmer's disease" or "sailor's disease" (figure 1). These lesions are usually squamous cell carcinomas and frequently develop keratoses and eczematoid areas on the nose, ears and cheeks. These rough, scaly areas—scurfy patches—are often the precursors of squamous cell carcinomas.

Squamous cell carcinomas may also develop in areas of postradiation dermatitis (figure 2). Ulcerations occurring in old burn scars are favorite sites for the development of squamous cell carcinomas. Irritation of papillomas and warts from shaving, epilation, rubbing or picking may instigate their change into carcinomas of either basal or squamous cell variety. Skin cancers may occur at any age, but there is a definite predilection for those individuals over 50 years of age. Basal cell carcinomas of the skin of the face are much more common than squamous cell cancers, accounting for over three-fourths of all cases in some reports.

A few general rules may be of some help: (1) All carcinomas arising on the vermilion and mucous membrane surfaces of the lip are squamous cell (figure 3). (2) Numerically, most epitheliomas of the skin of the face, ears, eyes, eyelids and nose are basal, at least in their beginning, but some of these may change to squamous cell later. (3) As in most rules, there is an exception—those lesions which develop in hyperkeratoses or scurfy patches on the skin of men who have had a lifetime exposure to sun and wind are squamous cell from the beginning and may arise spontaneously or as a change in a pre-existing keratosis or scar. (4) On the face of an individual, one lesion may develop into a basal cell carcinoma, while an apparently identical or neighboring lesion may develop into a squamous cell carcinoma, although it might first have been a basal cell lesion. (5) Contrary to most teachings, we regard basal cell carcinomas as elusive, invasive and highly malignant even though they do not metastasize (figure 6).

FIGURE 1. A 44 year old commercial fisherman showing characteristic skin changes as seen in farmer's or sailor's disease. His hair and beard are blond; his skin is thin and dry after many years' exposure to the sun, wind and salt spray.
a. There are many areas of hyperkeratosis and early squamous cell carcinoma of the forehead, cheek and neck bilaterally.
b. The involved areas of both sides of the face were excised widely and resurfaced with heavy split-skin grafts. Postoperative photograph, taken two years later, shows progressive changes occurring on the nose and the maxillary rim of the graft.

FIGURE 2. This 48 year old woman had received extensive radiation therapy approximately 13 years previously for the treatment of a carcinoma of the parotid gland.
a. Ulceration and necrosis began approximately one year before this photograph was taken. Biopsy of the margins and depth revealed a squamous cell carcinoma.
b. The entire area was excised widely and the defect repaired, using a flap from the nape of the neck. Postoperative photograph was taken approximately two years later.

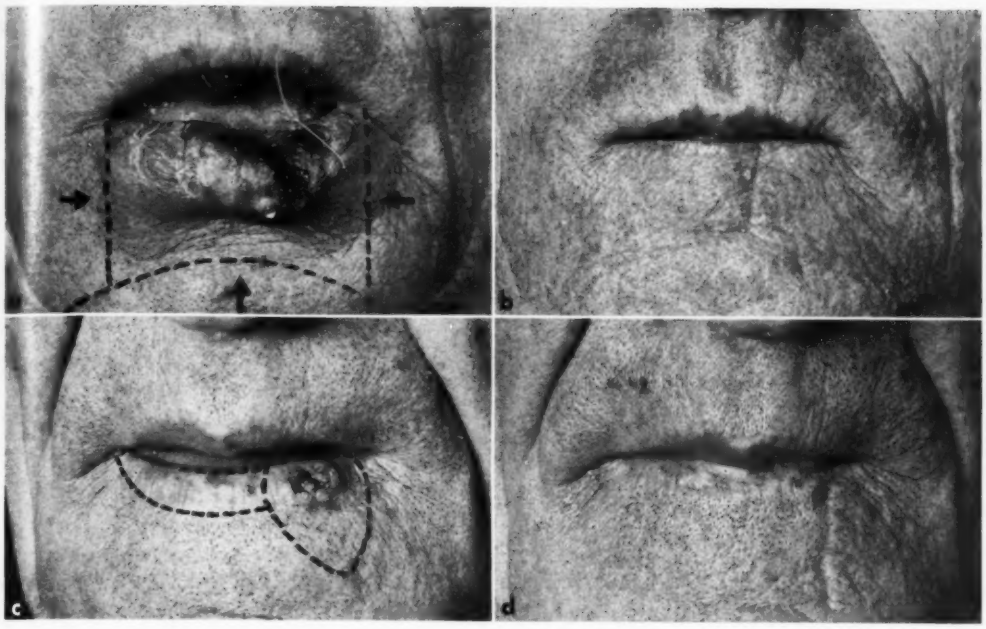


FIGURE 3a. Advanced squamous cell carcinoma of the lip in a 45 year old man which began approximately one year previously in a so-called nicotine blister.
b. The lower lip was removed and reconstructed primarily by advancing the cheeks medially. A left-sided radical neck dissection was performed at the same time. The right side of the neck was dissected six weeks later. Bilateral neck dissection was mandatory because of enlarged nodes in the submental region and both sides of the neck. Metastases were found on the left side, but were more numerous on the right. Enlarged nodes along the lines of lymphatic spread from a primary lesion are treated as possible metastases until proved otherwise.
c. An early carcinoma arising in an area of leukoplakia.
d. A wide block excision of the lesion was performed together with a "retread" of the entire lip.

Pathology

While no one can say just how any cancer will grow, there are some general principles or rules which may serve as helpful guides. The characteristic histologic feature of the malignant epithelial cell is its power of unlimited multiplication and its proneness to break through the normal limiting basement membrane and invade the subepithelial tissues along the lines of least resistance. Structurally, these cells are anaplastic and tend to revert to an embryonal form. Generally speaking, the more they differ from the normal structure and the nearer they approach the embryonal type, the more malignant is the growth. When the variation is slight, the degree of malignancy may be low. When the variation is marked, the degree of malignancy and invasiveness may be high. On this basis of the extent of the differentiation of the cells, that is, their ability to resemble and mimic the normal tissue from which they originate, Broders[8] grouped the various types of carcinoma into four grades. Grade I carcinoma is the least malignant because less than 25 per cent of the cells are undifferentiated. Grade IV carcinomas are the most malignant, because most of the cells are undifferentiated and only 25 per cent or less resemble the parent cells. In between are found grades II and III, grade II being less malignant, and grade III more malignant. It should be borne in mind, however, that this is a microscopic pathologic classification of cell differentiation and that virulence and evident activity of

growth are by no means synonymous, either clinically or by Broders' grading system.

Basal Cell Carcinomas

We regard basal cell carcinomas as treacherous, elusive and highly malignant, even though they do not metastasize to distant parts. These lesions appear and behave like benign lesions in their early stages, but unless removed widely, they will recur and destroy everything in their path of invasion.

Basal cell carcinomas arise most frequently in the central or so-called seborrheic areas of the face. Many lesions, both clinically and microscopically, seem to have their origin in sebaceous adenomas or plugged sebaceous glands. Basal cell carcinomas develop at an earlier age than squamous cell carcinomas. Early lesions rarely show rapid growth; in fact, they may appear to be quite indolent. There is no pain or discomfort and, hence, it not infrequently happens that patients will defer seeking advice until the lesion and disease are well advanced.

The appearance of an early lesion is quite characteristic (figure 4); it may resemble a small shirt button in that there is a firm, slightly elevated edge which may surround the lesion either completely or partially. The edge may be pearly or gray-blue in color and may have a scalloped appearance (figure 7c). The ulceration in the center is shallow. There is little, if any, surrounding induration, and so the lesion looks and feels like a button. However, striking variations in the clinical picture may be encountered. While slow growth and progression is the general rule, any rapid change should be acted on promptly because, as stated previously, a rapid change may be suggestive of change from a basal cell lesion to a basosquamous or a pure squamous cell carcinoma.

We refer to the primary lesion just described as button-type basal cell carcinoma. However, there are two other types which should be borne in mind also. The field fire basal cell lesion is a large, flat lesion with an active edge surrounding a central scarred area. Its shape may be serpiginous and the peripheral manner of spread has been compared to a fire in a field. The edges are active and spreading, whereas the central area may seem (often falsely) to have burned itself out (figure 5).

The third type of basal cell lesion is the highly invasive basal cell carcinoma, or rodent ulcer. This is one of the most difficult lesions to eradicate and, hence, one of the most dangerous. The surface lesion may appear somewhat like the button carcinoma. However, even though the surface lesion may appear quite innocuous, there is extensive invasion in and beneath the skin—hence the term submarine or iceberg type of progression and spread. What is actually seen on the surface may bear little resemblance to what is found beneath it (figure 6).

Not uncommonly, new or young house officers are appointed to remove basal cell lesions. This may be a dangerous practice unless the individual is cognizant of the facts and principles outlined and unless he remembers that in dealing with every carcinoma a life is actually at stake and that each incurable or inoperable surface carcinoma was, at one time, a small, seemingly insignificant lesion. A favorite and dangerous site for the development of basal cell carcinomas is along the lower eyelid and the inner canthus (figures 6 and 7b). In these locations especially, the lesions seem to have a special predilection for burrowing deeply, and unless they are removed early and completely, they may cause widespread destruction or even death.

Squamous Cell Carcinomas

Squamous cell carcinomas frequently develop in an area of previous skin change. They may begin as a thickening in an area of keratosis in farmer's or sailor's skin. A very early squamous cell cancer might be distinguished from a basal cell lesion by its bulkier growth, without the tendency to early central umbilication or ulceration seen in basal cell carcinomas. The difference between an early squamous cell carcinoma and a keratosis may not be apparent clinically until the lesion has increased in size. When this has taken place, much valuable time may have been lost because metastases may have occurred. Squa-

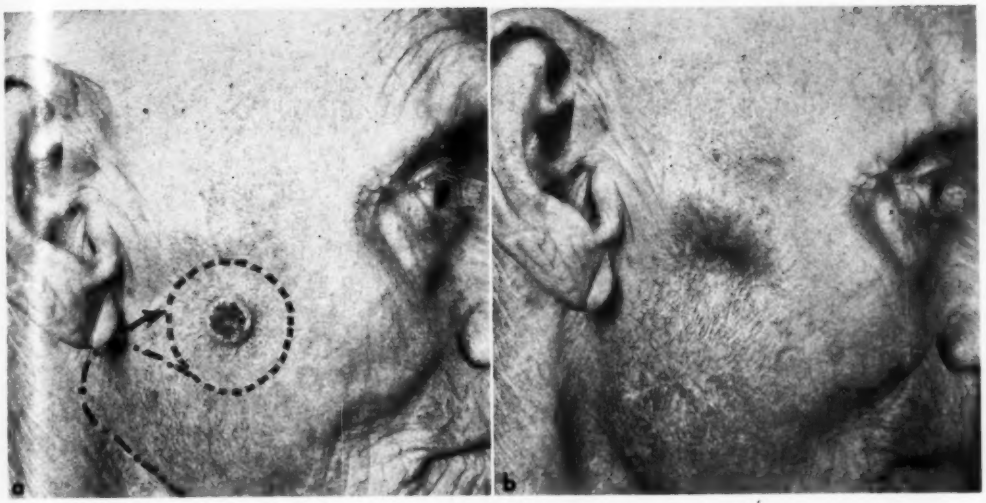


FIGURE 4a. Characteristic buttonlike basal cell carcinoma of the cheek. The edge is slightly elevated and gray-blue in color. The central area of ulceration or umbilication is shallow. The lesion was excised widely and the defect repaired (b) using a rotation flap as shown.

FIGURE 5a. Typical field fire basal cell carcinoma of the right cheek. The lesion had been present for almost three years. Clinically, the edges were active and spreading while the central area seemed to have burned itself out. However, pathologic studies disclosed activity in all sections.
b. The entire area was excised and resurfaced with a split graft.

FIGURE 6a. A highly invasive rodent ulcer basal cell carcinoma which began in the infraorbital region and progressed to involve the antrum and orbit.
b. Exenteration of the entire area was performed and, after allowing the defect to remain open for about six months to watch for residua, the area was then repaired by advancing the left neck and cheek skin superiorly. The patient is wearing a prosthetic eye.

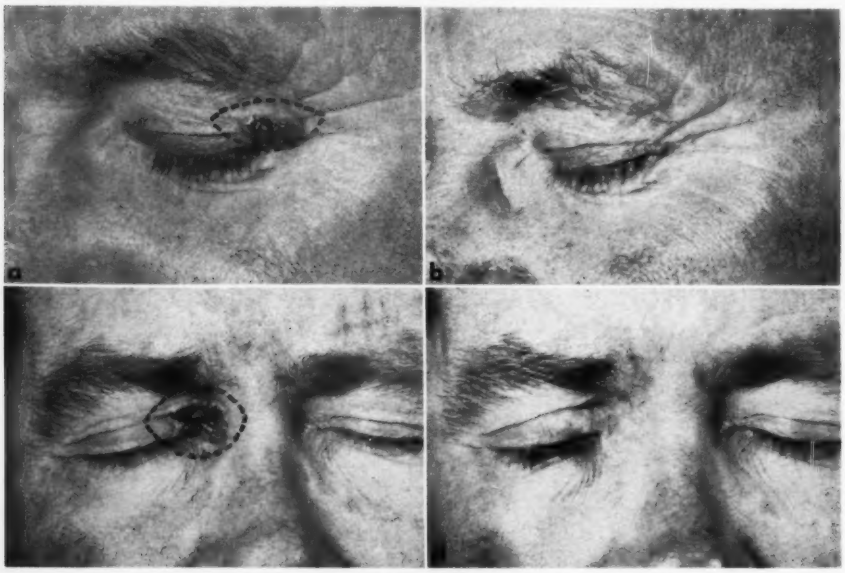


FIGURE 7a. Typical bulky squamous cell carcinoma of the upper lid.
b. Because of the suppleness of the tissues of the eyelid, wide excision and primary closure were possible.
c. Typical scalloped basal cell carcinoma occurring in an extremely dangerous location because of possible spread potential into the soft tissues of the lids and orbit.
d. The entire area was excised widely and, after obtaining pathologic clearance from studies of permanent (rather than frozen) sections, the defect was repaired, using a full-thickness postauricular graft.

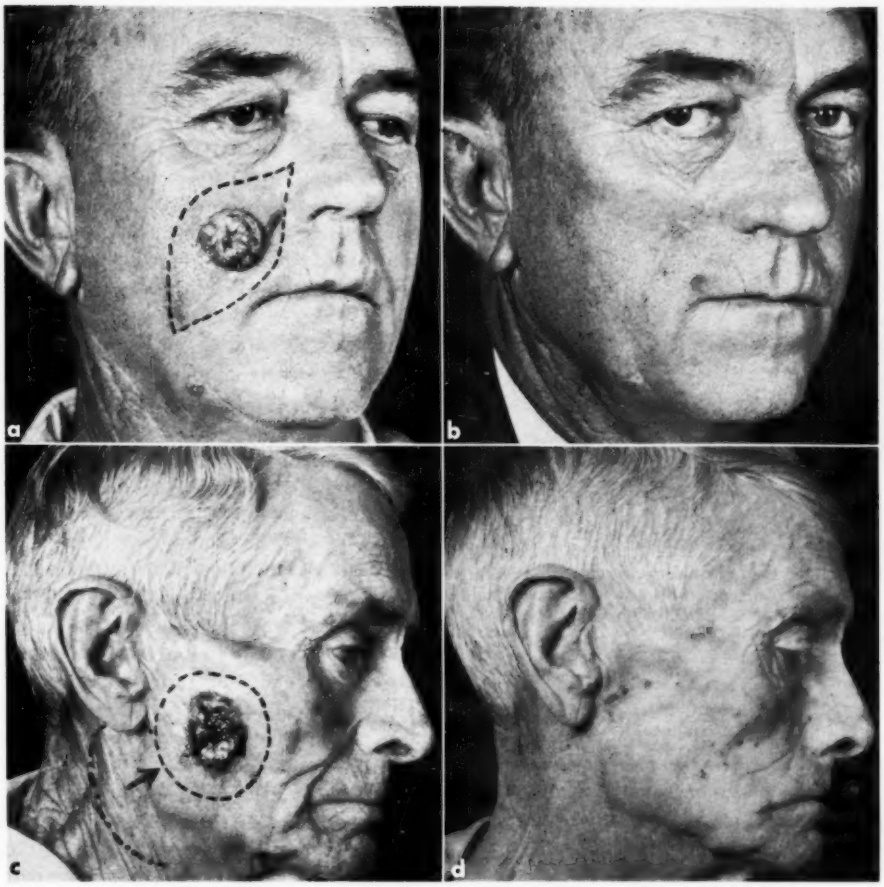


FIGURE 8a. A rapidly growing squamous cell carcinoma which began less than six months previously. The lesion was in a favorable location for wide excision and primary repair (b) without distorting the face. See figure 9.
c. Typical squamous cell carcinoma which had been present for more than a year. After the lesion was excised widely, the defect was repaired (d) at once using an adjacent flap from the lateral neck.

mous cell carcinomas usually increase quite rapidly in size and produce a bulky, cauliflowerlike growth which, at the same time, may burrow into the deeper tissues (figure 8). Necrotic portions may break off from the main tumor mass. Squamous cell carcinomas are very malignant from the beginning and metastasize quite early to the regional lymph nodes; hence the importance of early diagnosis and treatment. Pain is not a prominent symptom until late in the disease.

Squamous cell carcinomas arise from the outer or prickle-cell layer of the epidermis; hence the name "acanthoma," from the Greek, referring to a horn or a prickle. Pathologically, the lesions present pearl-like epithelial masses composed of groups of concentrically arranged squamous cells.

Other Malignant Lesions

True adenocarcinomas are quite rare. Melanomas are the most malignant of the skin tumors. Pack[9] has recently written a splendid review of his vast experience.

FIGURE 9. Position and direction for elliptical excisions on the face. Primary repair with essentially no residual scarring or distortion can be anticipated if one follows the normal creases and folds.

Sweat gland carcinomas first appear as elevated, hard plaques which later undergo central ulceration. The microscopic appearance is that of adenocarcinoma with sweat gland elements present. Metastases to the neck are uncommon.

Diagnosis and Treatment

Any persistent growth on the face, no matter how small, might be cancerous. As stated previously, all inoperable and incurable lesions were in the beginning small lesions.

If the lesion is small, total removal (excisional biopsy) is the procedure of choice (figure 9). If the lesion is large, a wedge-shaped biopsy using local anesthesia (injected at some distance from the lesion) should include not only part of the tumor mass but also an edge of skin, so that the pathologist may determine the degree of invasion. The final result depends on how early the patient seeks advice and the adequacy of the treatment administered. It is not so much the type of treatment selected, but the thoroughness of application. The aim of treatment is to eradicate the lesion completely and, at the same time, to leave a minimum of disturbance of function or disfigurement. Hence, early treatment is stressed again.

The choice among the available methods of treatment is secondary to the absolute requirement that whatever method is chosen, the treatment should be applied adequately and expertly. The results of treatment by radiation can be found in treatises on this subject. In general, the previously untreated basal cell carcinomas are quite amenable to radiation; squamous cell carcinomas are possibly less so. Radiation treatment should not be used on lesions arising in skin which is already damaged by actinic rays. One should not let his zeal carry him beyond the bounds of reason, for a life is at stake. If radiation therapy is selected, it should be given by a specialist and only after a biopsy has been obtained. Any lesion which has recurred following unsuccessful radiation should not be so treated again. One of the most encouraging signs is a new spirit of cooperation and mutual respect between surgeons and radiotherapists.

The surgical technic for the removal of tumors of the face is the same as that described elsewhere (figure 9). The tumor is circumscribed by oval incisions which encircle the lesion widely. A frozen section can be obtained within a few minutes. The pathologist will not only classify the tumor but will also advise the surgeon about the margins.

If the tumor is large and the wound margins cannot be approximated, the procedure to be adopted will be governed by the nature of the tumor and the reconstructive abilities of the surgeon. The use of a free graft or a contiguous flap may be the procedure of choice. With the advances in reconstructive surgery, large defects may be repaired immediately following radical excisions. The fundamental technic of surgical excision is the complete eradication of all malignant and potentially malignant tissue. The adequacy of excision should always be checked by frozen or permanent pathologic sections prior to reconstruction. One should be exceedingly careful not only to obtain sufficient peripheral margins, but also to verify depth margins.

Discussion and Conclusions

As outlined previously, this paper has been prepared for the practicing physician and student rather than the specialist. Our basic concept is to regard any ulcerative lesion of the face which persists for more than three or four weeks as carcinoma, until proved otherwise. The successful treatment of cancer here, as elsewhere, requires complete removal of the primary growth. The excision should be circumferentially wide with also a greater margin of tissue behind the growth, for that is the direction in which the most dangerous spread is apt to occur. Regardless of the histology of the growth, radical local removal demands normal tissue margins beyond all palpable and visible areas of involvement. All inoperable, incurable or advanced lesions at one time were small and seemingly insignificant lesions. A life is at stake when any carcinoma is treated, regardless of how small the primary lesion may be. One should never lose sight of the accepted principles on which our plan of treatment is based, nor the fact that each carcinoma is an individual problem. This is our creed.

REFERENCES

1. Eller, J. J. and Eller, W. D.: Tumors of the Skin: Benign and Malignant. Ed. 2. Philadelphia, Lea & Febiger, 1951.
2. Conway, H.: Tumors of the Skin. Springfield, Illinois, Charles C Thomas, 1956.
3. Ward, G. E. and Hendrick, J. W.: Diagnosis and Treatment of Tumors of the Head and Neck. Baltimore, The Williams & Wilkins Company, 1950.
4. Martin, H.: Surgery of Head and Neck Tumors. New York, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1957.
5. McDowell, F., Brown, J. B. and Fryer, M. P.: Surgery of Face, Mouth, and Jaws. St. Louis, The C. V. Mosby Company, 1954.
6. Blair, V. P., Moore, S. and Byars, L. T.: Cancer of the Face and Mouth. St. Louis, The C. V. Mosby Company, 1941.
7. Traub, E. F.: Diagnosis and treatment of carcinoma of the eyelids. J.A.M.A. 154:9-12 (January 2) 1954.
8. Broders, A. C.: Practical points on the microscopic grading of carcinoma. New York J. Med. 32:667-671 (June 1) 1932.
9. Pack, G. T.: End results in the treatment of malignant melanoma; a later report. Surgery 46:447-460 (August) 1959.

Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-160; additional listings are on page 305.

Medical Electronics. By Edward J. Bukstein, Instructor of Advanced Electronics, Northwestern Television and Electronics Institute, Minneapolis. 168 pages, illustrated. 1959, Frederick Ungar Publishing Company, New York. $3.50.

Prosthetic Principles—Above Knee Amputations. By Miles H. Anderson, Ed.D., Director, John J. Bray, C.P., Associate Research Prosthetist, and Charles A. Hennessy, C.P., Associate Director, Prosthetics Education Project, University of California at Los Angeles School of Medicine, Los Angeles. 331 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $10.00.

Genetics and Cancer. A collection of papers presented at the thirteenth annual symposium on fundamental cancer research, 1959. Edited by the staff of The University of Texas M. D. Anderson Hospital and Tumor Institute. Houston. 459 pages, illustrated. 1959, University of Texas Press, Austin. $8.50.

Hypnosis in Anesthesiology. By Milton J. Marmer, M.D., Chairman, Department of Anesthesia, Cedars of Lebanon Hospital, Los Angeles. 150 pages. 1959, Charles C Thomas, Springfield, Illinois. $6.75.

The Treatment of Bronchial Neoplasms. John Alexander Monograph Series. By Robert R. Shaw, M.D., Clinical Professor of Surgery, and Donald L. Paulson, M.D., Clinical Associate Professor of Surgery, University of Texas Southwestern Medical School, Dallas. 135 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $8.00.

The Megaloblastic Anemias. Modern Medical Monographs. By Victor Herbert, M.D., Instructor in Medicine. Harvard Medical School, Boston. No. 18. 162 pages, illustrated. 1959, Grune & Stratton, Inc., New York and London. $6.00.

Handbook of Circulation. Prepared under the direction of the Committee on the Handbook of Biological Data, Division of Biology and Agriculture, National Academy of Sciences, National Research Council. 393 pages. 1959, W. B. Saunders Company, Philadelphia and London. $7.50.

The Emergency Syndromes in Pediatric Practice. By Alfred J. Vignec, M.D., Clinical Professor of Pediatrics, New York University College of Medicine, and Medical Director and Pediatrician-in-Chief, New York Foundling Hospital, New York. 382 pages with 12 illustrations. 1959, Landsberger Medical Books, Inc., New York. $9.00.

De Magnete. By William Gilbert, M.D. Translated by P. Fleury Mottelay. 359 pages, illustrated. 1958, Dover Publications, Inc., New York. $2.00.

Early Treatment of Cancer of the Thyroid Gland

JOHN C. McCLINTOCK*

Albany Medical College, Albany, New York

JOHN C. McCLINTOCK

THE pathologist is usually the first to diagnose early cancer of the thyroid gland. Because many surgeons still feel that most nodular goiters should be removed, it is inevitable that most early thyroid cancers will be found in the laboratory. A predetermined plan of therapy therefore becomes important if the maximal number of long-term survivals is to be kept under observation. The variations of surgical procedures now in vogue, together with criteria for the surgical approach, are discussed in this presentation.

For the period January 1, 1946 through August 31, 1959, 142 cancers of the thyroid gland were operated on by me, and of this number, 97 or 68 per cent were diagnosed first by the pathologist. Forty-five were clinically self-evident cancers. The high percentage of laboratory-diagnosed thyroid malignancies is largely due to removal of apparently benign nodules which appeared to be solitary on clinical examination. Nowadays, many that come to operation have not responded to exogenous thyroid hormone or were found to be "cold" or occurred in young persons where cancer is more apt to be present in such a tumor. Although there may be a high degree of suspicion regarding the gross appearance of the tumors, the pathologist must establish the diagnosis by frozen or fixed sections.

Because it is most difficult to interpret findings in thyroid tissue and to separate benign from malignant disease in such tissue, not all pathologists are adept at giving a diagnosis from frozen sections. In fact, controversies have occurred when experienced pathologists examined the same fixed microscopic section. The difficulty of distinguishing benign from malignant thyroid lesions is illustrated by the following case. A clinically single nodule was removed by subtotal lobectomy from the right side of the patient's thyroid gland in 1937. Four pathologists, representing the top experience in our country, called the lesion benign. One pathologist and a surgeon were of the opinion that malignant change was present. In spite of many attempts to obtain follow-up in-

*Assistant Clinical Professor of Surgery, Albany Medical College and Albany Hospital, Albany, New York.

formation, nothing was heard of the patient until August 14, 1959. This is now known to be due to the fact that the patient became a Christian Scientist. She reappeared with the three year old lesion illustrated in figure 1. This proved at operation to be an implant which did not extend beneath the cervical fascia. The right thyroid lobe, however, contained a recurrence that had penetrated through the cricoid cartilage and upper three tracheal rings. No other metastases were demonstrated and the tracheal lesion has been treated with radioactive iodine. The architectural patterns of this cancer are seen in figures 2 and 3 which represent the original early lesion and the recurrence. This is the kind of experience that humbles pathologists and makes all of us wonder—why does thyroid cancer behave as it does?

A keen interest in the use of frozen sections helps to develop a high degree of accuracy in their use. Winship[1] has told me that his diagnoses from frozen sections have greater than 95 per cent accuracy when correlated with the interpretation of the permanent sections. Surgeons have to learn to rely on this type of experience in order to give the patient the best possible team-planned therapy. Conversely, surgeons can help to train pathologists by more frequent use of frozen sections.

Whether frozen or permanent sections are used to determine the surgical procedure, another area of disagreement is at once encountered. Some favor immediate prophylactic neck dissection, while others believe that neck dissection should be reserved for those patients with clinical evidence of lymph node spread. At present, I favor the latter course for the following reasons:

I have under observation a series of clinically benign tumors that now embraces 81 patients who were all treated by wide local excision, usually lobectomy, and in whom the pathologic diagnosis of cancer was established. In this group are 16 patients operated on 10 or more years ago and 26 whose surgical procedure was done 5 to 10 years ago; the remainder were treated in the last five years. Six patients have required additional therapy. Two with papillary tumors have had cervical lymph node dissections three and six years postoperatively and are now apparently free from disease. An additional papillary tumor recurred in one patient's chest and caused death 12 years postoperatively. In one patient with follicular-type thyroid cancer metastases developed three years postoperatively. These recurrences were cervical lymph node, abdominal wall and pulmonary deposits when the spread of disease was first noted. This patient is dead. Another patient died eight years following removal of a Hürthle cell cancer from his thyroid gland. Right shoulder and pulmonary metastases were present, the latter responsible for his demise. The sixth patient had pulmonary and cervical lymph node deposits that appeared eight years postoperatively and were treated with radioactive iodine. These six patients, so far, represent 7.4 per cent of this series, a figure which is in marked contrast to those reported by others.

Two reports[2,3] from the eastern seaboard indicate finding one or more positive lymph nodes when none could be palpated in 61 to 64 per cent of patients subjected to prophylactic neck dissection. Another account[4] from the Midwest reports that one-third of the patients with no clinical evidence of lymph node spread were found by neck dissections to have positive lymph nodes. Because of such findings many surgeons prefer immediate neck dissection which may be modified to leave the sternomastoid muscle and the internal jugular vein and need not include the submaxillary area if the operative findings warrant it. It is obvious that another 10 years of follow-up on these patients is required before valid conclusions can be drawn. It is equally apparent that continuation of both types of therapy under careful supervision is necessary so that accurate records will accrue and reliable reports result.

When the diagnosis of cancer can be made from the physical findings of hardness, irregularity or fixation of the tumor, or if cervical lymph node metastases are present when first seen, the patient can hardly be considered to harbor an early cancer. Yet, for the papillary type of thyroid tumor such a situation could be early in the natural life history of such neoplasms. The procedure of choice for these

FIGURE 1. Ulcerated tumor mass growing out from previous thyroidectomy scar.

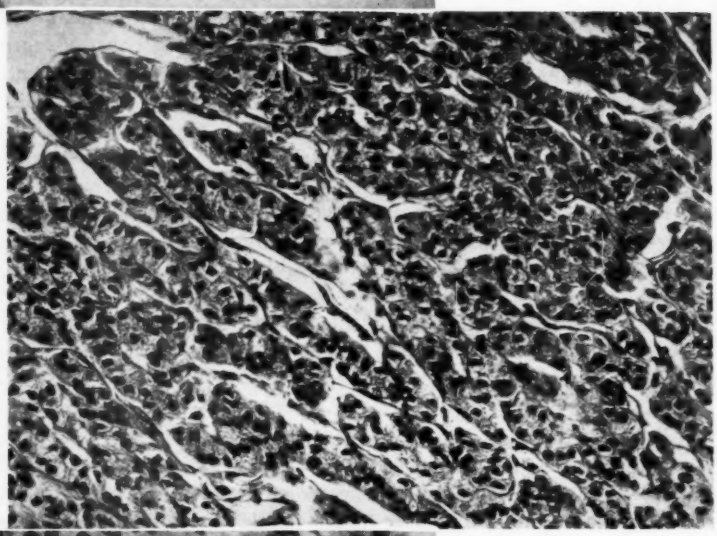


FIGURE 2. Photomicrograph of original tumor removed in 1937, showing cordlike pattern of the growth (x 220).

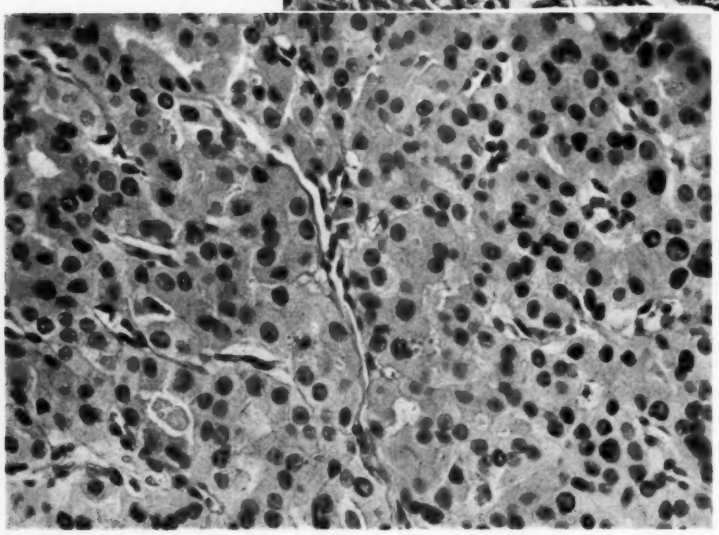


FIGURE 3. Photomicrograph of tumor in figure 1, demonstrating more clearly a Hürthle pattern (x 220).

(Figures 2 and 3 reproduced courtesy of the Armed Forces Institute of Pathology.)

patients is radical neck dissection of nearly the conventional type, with or without mediastinal dissection,[5] depending on the spread of the disease. Preservation of the sternomastoid muscle may be a possible variation. Near-total thyroidectomy, leaving the posterior capsule on the contralateral side, is a part of such dissection.

Near-total thyroidectomy is required because of the number of patients who have tumors with multiple foci of origin. Black, Kirk and Woolner,[6] in a paper presented before the American Goiter Association last spring, found multicentric foci in 18 per cent of 142 cases where both lobes were available for study. They suggested that where less than total lobectomy has been done on the primary side with subtotal resection of the contralateral lobe, the patient should be re-explored for removal of the remaining thyroid gland. Eleven of 17 patients so treated by them were found to have additional cancer in the remaining thyroid tissue. Two years ago at a panel discussion, Virginia Kneeland Frantz stated that the enthusiasm of the pathologist to do serial sections often determines how many patients with multiple foci of origin are uncovered. She found that more than 50 per cent did have such foci if searched for carefully.

Clark, White and Russell[7] reported a series of 120 patients where both lobes were available for study. In 79 of these patients the authors were responsible for the primary operation. Forty of the 79 were examined by routine pathologic methods which revealed that 30 per cent had cancer in the contralateral lobe. Thirty-nine of this group were studied by serially sectioning the entire thyroid gland and by this technic it was found that 87 per cent had bilateral cancer. For the entire group of 120 patients, cancer was observed grossly or microscopically in contralateral lobes or pericapsular lymph nodes in 54 per cent. It is obvious that serial section of the complete thyroid gland and adjacent tissues reveals a high percentage with disseminated cancer. Even when tissues studied by ordinary methods are included, the more than half of the cases with widespread glandular or periglandular disease is an alarming number. Clark and his co-workers do not refer to this dissemination as multiple foci of origin and they have found that all types of thyroid cancer have contributed to their series. In contrast to these reports are those of Crile, McNamara and Hazard[8] and Frazell and Foote[3] who reported that in 4 per cent and less than 1 per cent of cases, respectively, contralateral lesions developed.

It is curious and disconcerting to know that in my series of 81 patients who had only wide excision of their clinically benign tumors, not one single patient to date has returned with tumor in the contralateral lobe.

If I expand this group to include patients operated on by my predecessor but followed personally by me, such as the case previously cited, I have 107 patients who have been followed without evidence of contralateral spread. In this larger group, eight additional patients have had recurrent disease in cervical nodes or distant sites. Table 1 reveals the number of years between the original operation and the appearance of the recurrence. All patients were treated with radioactive iodine or by appropriate surgical procedures. Some of the patients are living apparently free from cancer, while others are known to have inaccessible disease that has not responded to any therapy. If I now add the deaths from thyroid cancer that have occurred in this study group, a total of 15 patients have had further trouble following the original operation. This 14 per cent is in marked contrast to the number of patients in whom recurrence would be expected to develop if the quoted statistics applied. This discrepancy requires an explanation which I hope the next 10 years of observation will provide. Incidentally, the papillary group in table 1 does not corroborate Crile[8] who feels from his experience that any patient who survives five years without evidence of papillary cancer has an excellent chance of remaining free from this disease.

Anker[9] has suggested a normal defense mechanism which operates to prevent the tendency of normal cells to become malignant. He postulates that such a mechanism is changeable in that it can lapse, allow formation of a macroscopic tumor, and then become operational later. Is it this defense that protects

TABLE 1

YEARS BETWEEN OPERATION FOR CANCER OF THYROID AND RECURRENCE

TYPE OF CANCER	CASE	PATIENTS LIVING		CASE	PATIENTS DEAD	
		Years between first operation and recurrence	*Years patient has lived since recurrence*		*Years between first operation and recurrence*	*Years patient lived after appearance of recurrence*
Papillary carcinoma	a	3	3	e	10	2
	b	6	3	f	18	6
	c	19	6			
	d	18	2			
Follicular carcinoma	g	11	2 (with disease)	m	3	3
	h	4	19 (with disease)			
	i	5	19 (with disease)			
	j	6	19			
	k	15	2			
	l	8	1			
Hürthle cell carcinoma	n	19	3 (with disease)	o	2	6

some patients from the high frequency of multicentric foci, and does it explain the discrepancies existing in those who had prophylactic neck dissections as opposed to those who did not? Leslie presented a similar point of view before the recent meeting of the British Association for the Advancement of Science. Will further investigation of these hypotheses lead us to a better method of controlling cancer?

Any discussion of the treatment of early thyroid cancer would not be complete without mention of the relationship of nodular goiter to malignant disease. This subject has been the cause of more controversy in the last 10 to 15 years than any other feature of thyroid cancer. But even here one can now discern areas of agreement that represent the advances wrought by such arguments. Sokal,[10] who has bitterly opposed mass removal of all thyroid nodules, concluded a recent article with these words: "It is clear, our efforts should be directed toward improving criteria for selection of patients for surgery rather than toward detection and extirpation of all thyroid nodules." In this direction, a great deal has already been accomplished.

The technic of scintigramming thyroid nodules to separate those which pick up more radioactive iodine than the surrounding thyroid tissue and are hence "hot" from tumors which are "cold" is one criterion for surgery. Cancer has been found in a significant number (20 per cent) of cold nodules.[11] The use of exogenous thyroid hormone in an amount sufficient to depress TSH and put the thyroid gland at rest has resulted in diminution in size or disappearance of some nodules. Most endocrinologists will pursue this method of therapy for three to four months, recommending surgery for the nodules that show no change in this period of time and continuing to treat those that have shown regression. Here is a second criterion for surgery. Single thyroid tumors in patients under 15 years of age are found to be cancer in 30 to 59 per cent of the cases,[12-14] depending on the author quoted. This high frequency of malignant disease, which ranks second as the cause of death for the 11 to 15 year olds, certainly seems sufficient reason to advise immediate removal of thyroid nodules at this age level. This is a third criterion for operation.

In this connection it is worthy of note that Winship,[1] who has collected the largest series

of cases of cancer of the thyroid in children under 15 years of age, has carefully reviewed 100 patients where knowledge of previous x-ray therapy was definitely known. In this group, over two-thirds had received external irradiation for tonsillar hypertrophy in infancy or early childhood or for thymus gland enlargement or other benign head and neck lesions. The late Dwight Clark[15] told me that 75 per cent of his thyroid cancer patients up to the age of 35 had received external irradiation for similar benign lesions. A history of external irradiation for any cause in infancy and childhood, therefore, becomes a fourth criterion for immediate removal of any thyroid nodule in patients up to the age of 35.

The future may well reveal other and better reasons for surgical intervention in cases of nodular goiter. It can be expected that an increasing number of cases will be diagnosed first by the pathologist if the criteria noted are followed. At present, those who have dealt with these problems most closely still feel justified in removing most thyroid tumors because we lack the ability to separate clearly those that are malignant from those that are not.

Summary

1. Today, criteria for selection of patients to undergo surgical removal of a thyroid nodule make it probable that the pathologist will be the first to definitely establish a diagnosis of malignancy.

2. Once the diagnosis of malignant disease is established, the surgeon must be prepared to follow an immediate program of radical surgery or one of watchful waiting and to keep all such patients under careful surveillance to determine the outcome.

3. Cancer of the thyroid gland can be one of the most malignant tumors of the body or one of the most enigmatic.

REFERENCES

1. Winship, T.: Personal communication to the author.
2. Meissner, W. A., Colcock, B. P. and Achenbach, H.: The pathologic evaluation of radical neck dissection for carcinoma of the thyroid gland. J. Clin. Endocrinol. 15:1432-1436 (November) 1955.
3. Frazell, E. L. and Foote, F. W., Jr.: Papillary cancer of the thyroid: A review of 25 years of experience. Cancer 11:895-922 (September-October) 1958.
4. Block, M. A., Miller, J. M. and Brush, B. E.: Place of radical neck surgery in thyroid carcinoma. A.M.A. Arch. Surg. 78:706-712 (May) 1959.
5. McClintock, J. C., Stranahan, A. and Alley, R. D.: Trans-sternal anterior mediastinal dissection for cancer of the thyroid. Am. Surgeon 20:726-733 (July) 1954.
6. Black, B. M., Kirk, T. A. and Woolner, L. B.: Multicentricity of papillary adenocarcinoma of the thyroid: Influence on treatment. (In press.)
7. Clark, R. L., White, E. C. and Russell, W. O.: Total thyroidectomy for cancer of the thyroid: Significance of intraglandular dissemination. Ann. Surg. 149:858-866 (June) 1959.
8. Crile, G., Jr., McNamara, J. M. and Hazard, J. B.: Results of treatment of papillary carcinoma of the thyroid. Surg. Gynec. & Obst. 109:315-320 (September) 1959.
9. Anker, H. S.: On the rate of incidence of malignant tumors. Perspectives Biol. Med. 1:436-438 (Summer) 1958.
10. Sokal, J. E.: The problem of malignancy in nodular goiter—recapitulation and challenge. J.A.M.A. 170:405-412 (May 23) 1959.
11. Greene, R.: Discrete nodules of the thyroid gland. with special reference to carcinoma. Ann. Roy. Coll. Surgeons England 21:73-89 (August) 1957.
12. Horn, R. C. and Ravdin, I. S.: Carcinoma of the thyroid gland in youth. J. Clin. Endocrinol. 11:1166-1178 (October) 1951.
13. Ward, R.: Malignant goiter; lessons to be learned from 20-year follow-up. West. J. Surg. 55:383-388 (July) 1947.
14. Dailey, M. E. and Lindsay, S.: Thyroid neoplasms in youth. J. Pediat. 36:460-465 (April) 1950.
15. Clark, D.: Personal communication to the author.

Early Cancer of the Oral Cavity With Special Reference to Cancer of the Tongue

ARNOLD J. KREMEN AND STUART W. ARHELGER*

University of Minnesota Medical School, Minneapolis

EARLY cancer, the theme of this symposium, is particularly meaningful in relation to the oral cavity because here, as with most peripheral cancers, the lesions are immediately available to inspection, palpation and simple, direct biopsy. Undue delay in establishing the nature of the lesion by the use of expensive, elaborate and time-consuming diagnostic methods, as is the case with visceral cancer, need not occur. Indeed, the appraisal of results of therapy of early favorable cancers of the oral cavity has been a prime factor in postulating and supporting the thesis that early diagnosis and prompt therapy of cancer can effectively reduce its appalling mortality.

ARNOLD J. KREMEN

The special problem of precancerous lesions, carcinoma *in situ* or noninvasive cancer, is, in large part, a local problem and can be dealt with by local excision. However, thorough histologic examination of the entire lesion is mandatory in order to avoid, if possible, the obvious error of relying on local methods of treating lesions containing both carcinoma *in situ* and invasive squamous-cell carcinoma.

Diffuse carcinoma *in situ* and diffuse leukoplakia of the oral mucosa present more difficult problems of management. In the light of present knowledge, it seems to be rational to perform local excision of all clinically suspicious areas of more pronounced thickening or ulceration or both, in addition to representative biopsies of the diffusely changed mucosa. If invasive carcinoma is not found and if the changes are truly diffuse, management consists of a program of interval examination which frequently implies interval biopsy as well. Indirect evidence continues to accumulate suggesting that elimination of tobacco, alcohol and nutritional and vitamin deficits is desirable and may well delay the onset or possibly prevent the development of invasive oral carcinoma.

In planning therapy for frankly invasive squamous-cell carcinoma, the classical surgical concept of primary growth, lymphatic spread and regional lymph node barrier should

*Departments of Surgery, University of Minnesota Medical School and Mount Sinai Hospital, Minneapolis, Minnesota.

be applied in its totality whenever it is anatomically practical. It is often presumptuous to assume that early diagnosis and early cancer are synonymous in a biologic sense.

Cancer of the Lip

The lip presents an ideal situation for early diagnosis of cancer. The lesion is immediately available and should soon catch the attention of the patient, his friends, family, physician or dentist for inspection, observation and biopsy. However, the excellent prognosis of early lip cancer, known to both the public and the medical profession, not infrequently may be employed to induce complacency and procrastination or to permit the utilization of less than adequate methods of therapy.

The treatment of early lip cancer is no longer an area of controversy. Adequate methods, both surgical and radiologic, are on hand and have repeatedly documented cure rates of from 90 to 95 per cent for favorable early lesions. However, it should be stressed that both methods call for experienced and expert judgment and methodology. Inept radiation can be as disastrous as crude and inadequate surgery, for if recurrences occur with either method, the favorable prognosis is forever lost and cure rates then drop 50 to 65 per cent.

An ideal, rigid and dogmatic plan of therapy for early cancer that will apply to all cases cannot be stated with confidence. There is great need for individualization of patients and for exercise of judgment and experience. Small, superficial lesions with a normal vermilion border can be equally well treated by irradiation or surgical excision, although it is our preference to excise these lesions with an adequate margin (1 cm.) of grossly normal tissue in all planes. We are reluctant to irradiate the lip in a patient under the age of 50 or in an individual whose occupation keeps him out-of-doors a major portion of the time. Thick lesions are preferentially treated by excision. Irradiation of such lesions not infrequently results in destruction of full thickness of the lip and produces a depressed fibrotic, sensitive zone of tissue, prone to injury by heat, cold, mechanical trauma and sunlight, which can be avoided by proper excision and plastic repair. Lesions near the commissures are more likely to metastasize and are better treated by immediate excision. Palpable lymph nodes in the presence of a primary cancer of the lip constitute an absolute contraindication to irradiation therapy of the primary growth. It is far preferable to excise the primary growth generously and be confident that this aspect of the disease is immediately eradicated, and then to proceed with a neck dissection soon thereafter.

The presence of marked atrophy or leukoplakia of the vermilion border of the lip with or without a concomitant cancer is best treated surgically. The so-called lip shave, modified to individual specifications in almost every surgical clinic dealing with these problems, is an effective means of replacing a worn-out cancerophilic area with a new, cosmetically acceptable surface. It is important to stress that all suspicious areas be subjected to biopsy in advance. Any area of cancer requires a more extensive, full-thickness V excision which can be done in conjunction with the lip shave (figure 1).

The management of early cancer of the lip cannot be considered as a purely local problem, because the threat of metastasis to cervical lymph nodes always remains. When this happens, we are no longer dealing with early cancer. Any definition of time, histology and size of lesion cannot preclude this threat. If the lymph nodes are palpable at the time of therapy to the primary lesion, there is uniform agreement that a complete neck dissection should be done. It is our practice, since such a procedure cannot practically be done in continuity with the primary growth, to delay the neck dissection for about two weeks after resecting the primary growth in the lip.

Accumulated experience does not support the practice of so-called elective neck dissections for cancer of the lip when the lymph nodes are not palpably enlarged. This should not be construed to apply to other intraoral cancer, particularly cancer of the tongue, where, as will be shown later, a strong plea for early neck dissection will be documented.

In cancer of the lip we are dealing with essentially a slow-growing, infiltrative, squa-

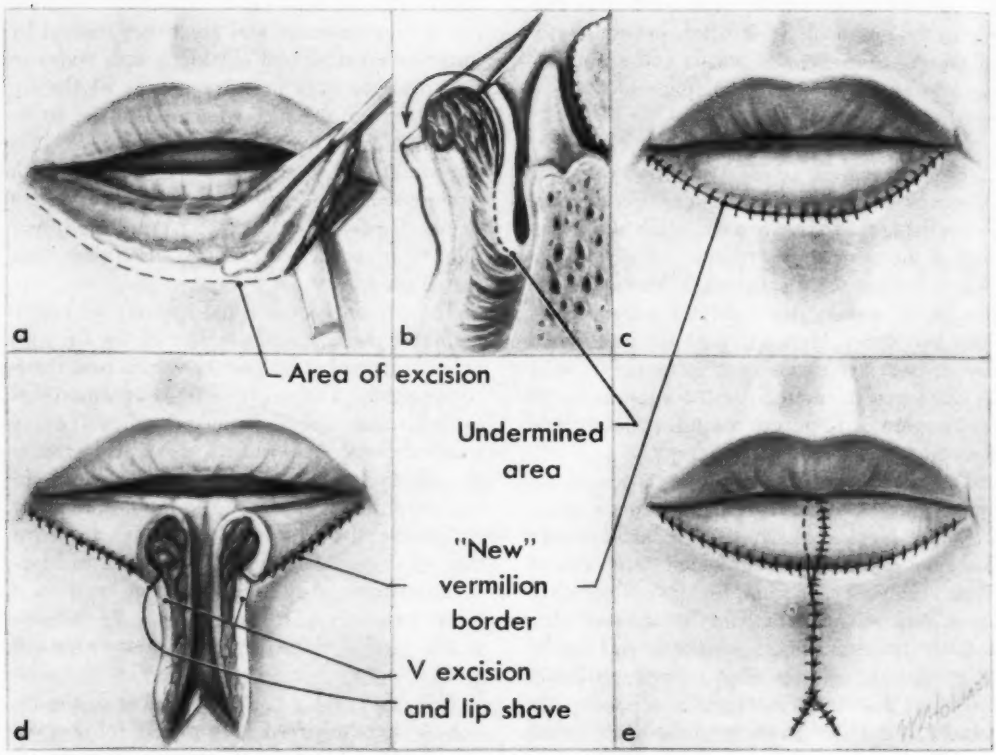


FIGURE 1a, b and c. Technic of lip shave. d and e. V excision of cancer plus lip shave.

mous carcinoma which metastasizes late in the course of the disease. If routine elective neck dissections are performed in the absence of palpably enlarged lymph nodes, microscopically demonstrable metastases are found in only 10 to 12 per cent of the specimens. Indeed, for early cancer of the lip the incidence may be considerably lower. Martin, MacComb and Blady[1] found an increasing incidence of metastases to lymph nodes related to the size of the primary tumor, with metastases to nodes in 3 per cent of cancers up to 1 cm. in diameter, in 10 per cent of tumors 1 to 2 cm. in diameter, in 13 per cent of tumors 2 to 3 cm. in diameter, and 26 per cent node involvement in cancers over 3 cm. in diameter. It would, therefore, appear that for cancer of the lip routine neck dissections would result in an unacceptably high percentage of potentially unnecessary operations to justify the procedure.

In our opinion, a yield of positive lymph nodes of 25 per cent or greater should be demonstrated to warrant routine recommendation of neck dissection. Moreover, if the patients are cooperative and the physician is alert, the operation can be done when the cervical lymph nodes first become palpable, with very little loss of ultimate salvage, compared to the 50 per cent cure rate for elective or prophylactic neck dissection.[2] It is extremely important, therefore, that when such a policy is adopted, the patients are instructed to return for periodic follow-up examinations. Most of the deaths due to treatment failure of cancer of the lip are due to cervical metastases which have been allowed to progress to an inoperable state because of the patient's failure to return for follow-up, or because of medical ineptness in failing to appreciate early metastatic disease.

Cancer of the Tongue

Although cancer of the tongue occurs considerably less frequently than cancer of the lip, its serious nature is manifest by the fact that it causes more deaths than any other intraoral cancer.[3] Treatment of cancer of the tongue is still an area of controversy between surgeons and radiotherapists. Even among surgeons there is a lack of uniformity regarding the extent of surgery to the local lesion and the proper place of neck dissection in so-called early cancer.

Results of treatment of cancer of the tongue where aggressive en bloc cancer surgery has been routinely applied have not been available in large numbers to compare with the results of the more commonly practiced discontinuous method of destroying the local lesion by either radiation or local excision, followed by neck dissections when the nodes became palpable.

Anatomically, the tongue with its lymphatic drainage area lends itself nicely to the classical concept of excisional cancer surgery, namely, en bloc resection of the tongue, floor of the mouth, and cervical lymphatics. Regular application of this principle in the management of cancer of the tongue, as in the management of cancer of the breast, colon or rectum, is now yielding superior cure rates when compared with the older, more commonly used discontinuous methods of therapy.[4-6] In 1951, one of us (A. J. K.)[7] published a description of the operative procedures employed in the presently reported series. Similar procedures, varying in detail but embracing the concept of in-continuity resection of the tongue, floor of mouth and neck dissection, have been reported by others.[5,6,8] If this trend of improved results continues in our experience and in the reported experiences of others, are we justified in advocating this plan for regular practice in so-called early cancer of the tongue? The over-all mortality of the extended operation has been acceptable. In our series, there have been two postoperative deaths in 38 patients, a 5 per cent mortality rate. Both deaths occurred in cases involving positive lymph nodes. One man died of multiple pulmonary emboli, the other of renal failure. Since these are the hazards of treating any group of elderly patients, either fatality could have happened with any mode of therapy. The neck dissection, aside from the scar and some shoulder stiffness, poses very little disability for these patients and rarely interferes with their postoperative rehabilitation. The hemiglossectomy and resection of the floor of the mouth, if one has to extend the resection posterior to the tonsillar pillars to any extent, does produce some impairment of the finer nuances of speech and occasional temporary problems in deglutition. For the most part, however, these problems have been quite minor and a majority of patients have been gratified with the result. All patients who were gainfully employed before their operation were able to return to their previous occupations. Cosmetically, the facial appearance with preservation of the mandible is essentially unchanged.

In contradistinction to the lip, where early cancer is essentially a slow-growing and reliably predictable lesion, frank invasive cancer of the tongue, even though small in size and historically of recent origin, gives no assurance that it is early or favorable in a biologic sense. In the past several years we have seen two patients (not included in this series) whose presenting complaints were enlarged, unilateral deep cervical lymph nodes. Biopsy of the nodes revealed metastatic squamous carcinoma. When careful examination of the mouth, larynx and pharynx failed to reveal a primary lesion, both patients were treated by radical neck dissection. During subsequent follow-up of 15 and 17 months, respectively, the primary cancers appeared on the tongue and were large enough to be palpated and proved by biopsy. Both tongue lesions had produced gross metastatic disease while completely asymptomatic and not large enough to be found on careful examination. In these instances, certainly, the criterion of size bore no relation to early cancer in a biologic sense, and the duration of symptoms was perfectly meaningless.

In a group of 16 patients with primary cancer of the tongue less than 2 cm. in diameter (table 1), seven patients, or 44 per cent, had

TABLE 1

LOCAL TONGUE LESION LESS THAN 2 CM. IN DIAMETER

	TOTAL CASES	HISTOLOGIC CANCER		PER CENT INVOLVEMENT
		Positive	*Negative*	
Clinically negative nodes	11	5	6	45
Clinically positive nodes	5	2	3	40
TOTAL	16	7	9	44

TABLE 2

LYMPH NODE INVOLVEMENT AT INITIAL OPERATION
ALL CASES

	TOTAL CASES	HISTOLOGIC CANCER		PER CENT INVOLVEMENT
		Positive	*Negative*	
Clinically negative nodes	26	12	14	46
Clinically palpable nodes	12	7	5	59
TOTAL	38	19	19	50

demonstrable lymph node metastases when treated by routine resection of the primary tongue lesion combined with in-continuity neck dissection. In this series, 11 patients had nonpalpable cervical lymph nodes for a similar percentage involvement. These findings are quite similar to the observations in a larger group of 38 cases of operable tongue cancer treated surgically in the same fashion (table 2). Here, the over-all demonstrated incidence of lymph node metastases was 50 per cent, and in the clinically negative 26 patients, 12, or 46 per cent, had histologically demonstrable metastatic cancer in one or more regional lymph nodes. Actually, the yield may indeed be higher, as these results were obtained by careful sampling of gross lymph nodes in the specimen, but the specimens were neither cleared nor serially sectioned. Where such studies have been done elsewhere, the microscopic demonstration of foci of metastases has shown an increase of from 10 to 30 per cent.[9]

TABLE 3

THREE YEAR RESULTS
ALL CASES OPERATED ON

	DEAD OR RECURRENCE	ALIVE AND FREE FROM DISEASE	
	Number	*Number*	*Per cent*
Total cases	10	23	70
Pathologically negative nodes	1	15	93
Pathologically positive nodes	9	8	47

With these findings in mind one cannot with confidence consider small, invasive cancers of the tongue as a local disease alone. It would seem wise, therefore, to deal with small cancers of the tongue as we do with similar cancers elsewhere in the body and to employ a complete cancer operation in every instance. We believe we will have more to show for our efforts in terms of ultimate cures if we spend more of our energies doing complete cancer operations for favorably appearing lesions rather than reserving our best operations only for the obviously advanced growth.

Results of Treatment

Since 1949, all cases of cancer of the tongue in the Department of Surgery at the

TABLE 4

FIVE YEAR RESULTS
ALL CASES OPERATED ON

	DEAD OR RECURRENCE	ALIVE AND FREE FROM DISEASE	
	Number	*Number*	*Per cent*
Total cases	10	21	68
Pathologically negative nodes	1	14	93
Pathologically positive nodes	9	7	44

University of Minnesota and in our private practice have been treated by primary in-continuity resection of tongue, floor of mouth and neck dissection, as described in 1951.[7] Some additional patients coming to the University Hospitals not under the jurisdiction of the surgery department or for reasons of inoperability were not treated in this fashion. These are not included in this report. All patients operated on have been followed. There are available for follow-up study 33 patients treated more than three years ago and 31 patients operated on more than five years ago.

Criteria for operability were as follows:

1. Lesions were confined to one-half of the tongue or floor of the mouth or both and did not grossly extend beyond the midline.

2. Lesions arising primarily at the base of the tongue were excluded because they are highly undifferentiated growths and ordinarily are quite sensitive to irradiation. However, resections as far posterior as the epiglottis have been carried out in the operated group of patients.

3. Clinical evidence of regional lymphatic involvement was not considered a contraindication to surgery unless the nodes were massively enlarged and fixed.

4. Age was not a consideration. Patients up to 80 years of age are included in the operated group.

Table 3 records the results of surgery at the three year interval. Of 33 patients operated on, 23, or 70 per cent, were alive and free of recurrence. In the group of 17 patients with metastases to the cervical nodes, eight, or 47 per cent, were alive and free of recurrence. Included among the failures in this group are the only two postoperative deaths of the series. Sixteen patients had no evidence of metastatic disease, as shown by the resected specimens; in this group there was only one failure, a recurrence of cancer beside the epiglottis. Fifteen of these patients, or 93 per cent, were alive and free of the disease after three years. That a three year appraisal of results in cancer of the tongue is a reliable figure is supported by table 4 where the five year results in only a slightly smaller group of 31 patients reveal identical cure rates.

Although this series is not yet large enough to be completely convincing, these data strongly suggest that operable cancer of the tongue, if treated aggressively by a complete cancer operation, will yield cure rates considerably in excess of those usually reported for this disease. Indeed, it would appear that for the tongue one can obtain cure rates heretofore only associated with cancer of the lip.

REFERENCES

1. MARTIN, H. E., MACCOMB, W. S. and BLADY, J. V.: Cancer of the lip. Ann. Surg. 114:226 (August); 341 (September) 1941.
2. MODLIN, J.: Neck dissections in cancer of the lower lip; five-year results in 179 patients. Surgery 28:404-412 (August) 1950.
3. Cancer of the tongue. Texas Cancer Bull. 1:15 (January-February) 1948.
4. KREMEN, A. J.: Results of surgical treatment of cancer of the tongue. Surgery 39:49-53 (January) 1956.
5. SOUTHWICK, H. W., OTTEN, J. W. and SLAUGHTER, D. P.: Treatment of squamous cell carcinoma of the tongue. *Ibid.* 43:313-318 (February) 1958.
6. WARD, G. E., EDGERTON, M. T., CHAMBERS, R. G. and MCKEE, D. M.: Cancer of the oral cavity and pharynx and results of treatment by means of the composite operation (in continuity with radical neck dissection). Ann. Surg. 150:202-220 (August) 1959.
7. KREMEN, A. J.: Cancer of the tongue, a surgical technique for a primary combined en bloc resection of tongue, floor of mouth and cervical lymphatics. Surgery 30:227-240 (July) 1951.
8. WARD, G. E. and ROBBEN, J. O.: A composite operation for radical neck dissection and removal of cancer of the mouth. Cancer 4:98-109 (January) 1951.
9. SAPHIR, O. and AMROMIN, G. D.: Obscure axillary lymph-node metastasis in carcinoma of the breast. *Ibid.* 1:238-241 (July) 1948.

To Our Subscribers:

In order to offer a complete presentation of the papers from the Scientific Session of the American Cancer Society in this special issue, it was necessary to omit some of our regular features this month. However, all of these features—the Scientific Exhibit, Nutrition in Clinical Medicine, Clinicopathologic Conference, Self-help Devices, Clinical Studies, Editorials—and the full content of clinical articles will appear as usual in the April issue.

THE EDITORS

performance

genitourinary infection. Roberts, M. S.; Seneca, H., and Lattimer, J. K.,[1] New York, N. Y.—Ninety-one per cent of the Gram-positive and 27 per cent of the Gram-negative, among 66 organisms cultured from genitourinary infection, responded to DECLOMYCIN. Serum antibiotic activity was found three times greater than with tetracycline.

toleration. Boger, W. P., and Gavin, J. J.,[2] Norristown, Pennsylvania—Side effects with DECLOMYCIN were minimal. When dosage was 0.5 to 1 Gm. daily in divided doses, only two of 82 patients exhibited nausea.

activity level sustentation. Kunin, C. M.; Dornbush, A. C., and Finland, M.,[3] Boston, Massachusetts—Of the four tetracycline analogues, DECLOMYCIN Demethylchlortetracycline showed the longest sustained activity levels in the blood.

gonococcal infection. Marmell, M., and Prigot, A.,[4] New York, N. Y.—Of 63 cases of gonorrhea, 61 promptly responded after short courses of DECLOMYCIN. Therapeutic effect was found equal to that of intramuscular penicillin.

bronchopulmonary infection. Perry, D. M.; Hall, G. A., and Kirby, W. M. M.,[5] Seattle, Washington—Of 30 cases of acute bacterial pneumonia, all were afebrile following two to 10 days of treatment with DECLOMYCIN. Results were good in 21.... All of six patients with acute bronchitis responded promptly.

pediatric infection. Fujii, R.; Ichihashi, H.; Minamitani, M.; Konno, M., and Ishibashi, T.,[6] Tokyo, Japan—In 309 pediatric patients with various infections, DECLOMYCIN was effective in 75 per cent.

urogenital infection. Vineyard, J. P.; Hogan, J., and Sanford, J. P.,[7] Dallas, Texas—Clinical response in pyelonephritis correlated well with results of *in vitro* sensitivity tests, which showed some strains of *A. aerogenes*, Proteus and Pseudomonas more susceptible to DECLOMYCIN Demethylchlortetracycline than to its analogues.

pneumonia. Duke, C. J.; Katz, S., and Donohoe, R. F.,[8] Washington, D. C.—Results were satisfactory in all but two of 32 cases of acute bacterial pneumonia, of which only 11 were uncomplicated. No side effects were observed.

brucellosis. Chávez Max G.,[9] Mexico, D. F., Mexico—All of nine patients with *Br. melitensis* infection were afebrile after five days on DECLOMYCIN. Blood cultures were negative in all cases on the 20th day. Side effects were limited to slight temperature increases which abated in four days.

pustular dermatosis. Blau, S., and Kanof, N. B.,[10] New York, N. Y.—Results with DECLOMYCIN were excellent in both of two cases of impetigo, one of two cases of folliculitis, six of nine cases of furunculosis, all of three cases of acne rosacea and 26 of 45 cases of acne vulgaris. Overall, results were excellent or good in 85 per cent.

antibacterial spectrum. Finland, M.; Hirsch, H. A., and Kunin, C. M.,[11] Boston, Massachusetts—DECLOMYCIN Demethylchlortetracycline was found the most effective of the tetracycline analogues against two-thirds of 680 normally sensitive strains of 15 separate species.

the over-all picture. Combined results reported by 210 clinical investigators[12]—DECLOMYCIN produced a favorable response (cured or improved) in 87 per cent of 1,904 patients. Two-thirds of the patients received one capsule every six hours. Treatment was continued for as long as 180 days, but was between three and eight days in most. Side effects were seen in 9.9 per cent, but necessitated discontinuance of treatment in only 1.8 per cent.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

New *for your armamentarium*

Information published in this department is supplied by the manufacturers of the products described.

• MICROLITER PIPETS

DESCRIPTION: Featuring bold red capacity markings which are a permanent part of the glass, these PYREX® microliter (lambda) pipets are designed for radiochemistry, electrophoresis and chromatography, as well as for general microbiologic and microchemical applications. The extremely fine graduation line permits accurate readings. An economy line of microliter pipets with standard capacity markings is also available. Both types of pipets are produced with capacities of from 1 through 500 μl. A re-usable storage case is supplied which holds a dozen pipets.
PRODUCER: Corning Glass Works, Corning, N.Y.

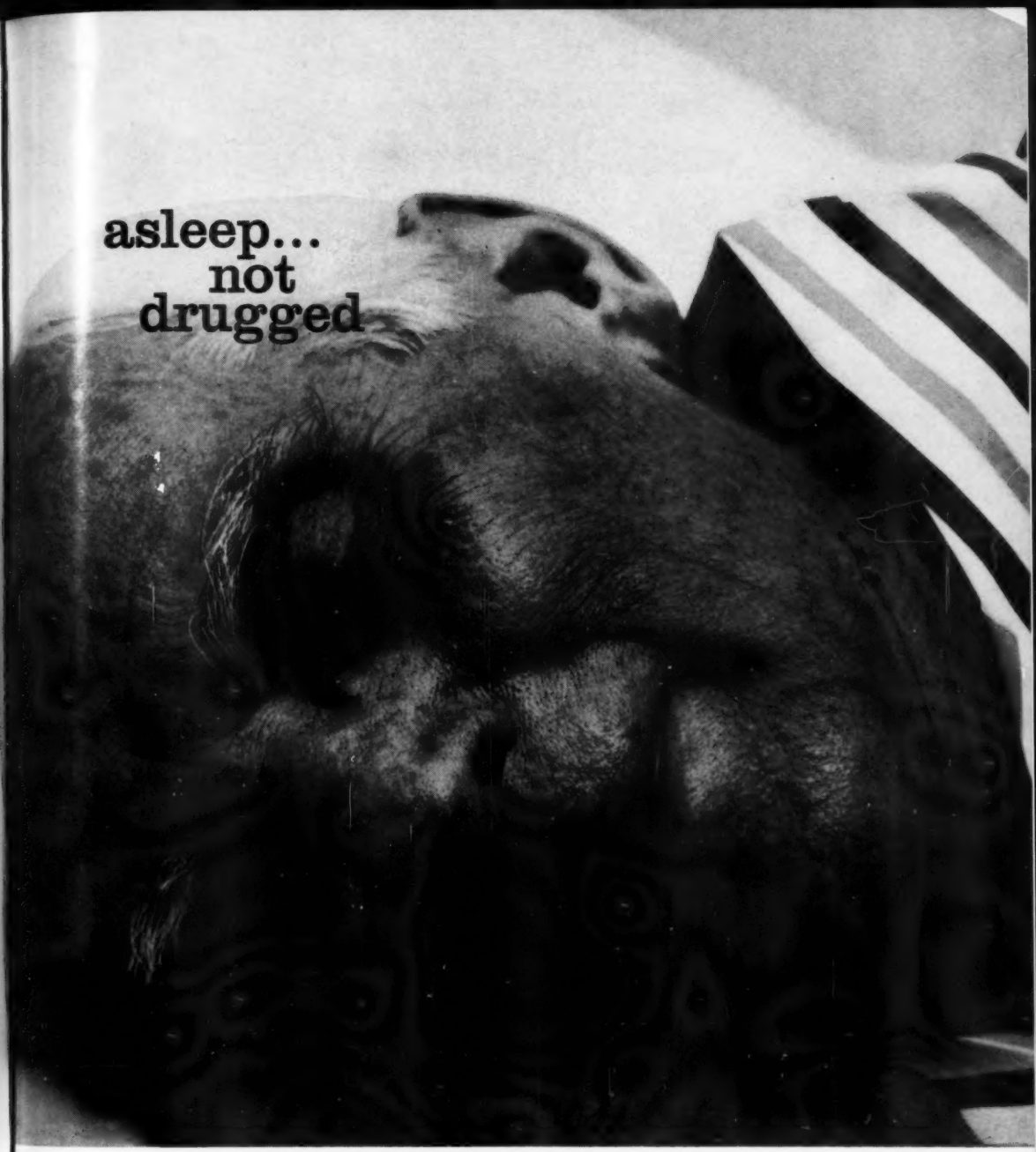
• URSINUS

PURPOSE: To treat sinusitis and other respiratory conditions.
COMPOSITION: Each Inlay-Tab contains 300 mg. CALURIN® (calcium acetylsalicylate carbamide), which is equivalent to 5 gr. aspirin, and 50 mg. TRIAMINIC®.
DOSAGE AND ADMINISTRATION: For adults, 1 or 2 Inlay-Tabs every four to six hours; for children 6 to 12 years old, ½ to 1 Inlay-Tab every six hours.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Smith-Dorsey, a division of The Wander Company, Lincoln.

• MYSTECLIN®-F FOR SYRUP AND AQUEOUS DROPS

PURPOSE: Antibacterial therapy and antimonilial prophylaxis.
COMPOSITION: Syrup: 125 mg. phosphate-potentiated tetracycline and 25 mg. amphotericin B. Aqueous drops: 100 mg. phosphate-potentiated tetracycline and 20 mg. amphotericin B.
HOW SUPPLIED: Syrup: in bottles for reconstitution to 60 cc. with 35 cc. of water. Aqueous drops: in bottles for reconstitution to 10 cc. with 6.5 cc. of water.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

(Continued on page A-132)



For a night of deep, refreshing sleep and a lively awakening... Noludar 300... one capsule at bedtime promises 6 to 8 hours of undisturbed sleep without risk of habituation, without barbiturate "hangover," toxicity or even minor side effects. Try Noludar 300 for your next patient with a sleep problem. One capsule at bedtime. Chances are he'll tell you

"I slept like a log"

NOLUDAR® 300

brand of methyprylon

300-mg capsules

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

• CARDI-O-MITE

DESCRIPTION: Weighing only 17 lb., this portable electrocardiograph provides direct-writing and full-size recordings. A high rejection ratio of AC interference and a high-frequency response permit audible monitoring of the heart signal as well as visual stylus monitoring without using paper. An oscilloscope jack is provided to allow use of available oscilloscope equipment. The instrument is available in single-speed and dual-speed models. The latter provides recording speeds of 25 to 50 mm. per second, making possible a double-size horizontal enlargement. The unit is of wood with metallic surfaces and a fabric-textured base. The vinyl plastic carrying case has a zipper closure. Dimensions are 11½ by 7½ by 6½ in.
PRODUCER: Beck-Lee Corporation, Chicago.

• LIQUI-CEE

PURPOSE: Vitamin C therapy.
COMPOSITION: Each teaspoonful (5 cc.) contains 1 gm. ascorbic acid in a buffered aqueous vehicle.
DOSAGE AND ADMINISTRATION: ½ teaspoonful, or as prescribed.
HOW SUPPLIED: 4 oz. bottles.
PRODUCER: U. S. Standard Products Company, Mount Prospect, Ill.

• ATROPINE INJECTION

PURPOSE: Anticholinergic.
COMPOSITION: Each cubic centimeter contains 0.5 mg. atropine sulfate.
DOSAGE AND ADMINISTRATION: 0.5 mg. given intravenously, intramuscularly or subcutaneously.
HOW SUPPLIED: 20 cc. multi-dose vials.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y.

• ERYTHROCIN®-I.M.

PURPOSE: Treatment of infections caused by erythromycin-sensitive organisms.
COMPOSITION: Erythromycin ethyl succinate dissolved in polyethylene glycol.
CAUTION: This product must not be administered intravenously or subcutaneously, and it should not be given to patients who have exhibited a reaction to BUTESIN®.
DOSAGE AND ADMINISTRATION: Recommended dose for adults is 100 mg.; for children, dose is reduced in proportion to age and weight. The interval between injections may be selected according to the severity of the infection.
HOW SUPPLIED: In ABBOJECT® disposable syringes containing 1 and 2 ml. Erythrocin-I.M.
PRODUCER: Abbott Laboratories, North Chicago.

• ORNADE

PURPOSE: Nasal decongestant.
COMPOSITION: Each SPANSULE® capsule contains:

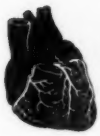
Isopropamide iodide	2.5 mg.
Phenylpropanolamine hydrochloride	50 mg.
Chlorprophenpyridamine maleate (TELDRIN®)	8 mg.

CAUTION: This drug should not be given to patients with glaucoma or prostatic hypertrophy. Use with caution in cases of severe hypertension.
DOSAGE AND ADMINISTRATION: 1 capsule every 12 hours.
HOW SUPPLIED: Bottles of 30.
PRODUCER: Smith, Kline & French Laboratories, Philadelphia.

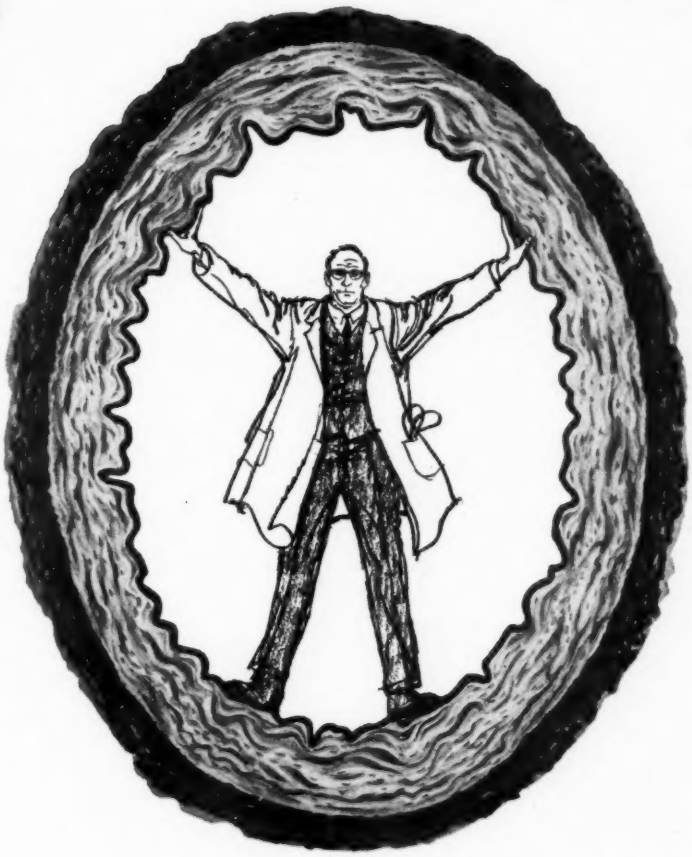
• PENTIDS® 400 FOR SYRUP
(New Formula)

PURPOSE: Antibiotic.
COMPOSITION: Each teaspoonful (5 cc.) of reconstituted solution contains 400,000 units of potassium penicillin G.
DOSAGE AND ADMINISTRATION: 1 teaspoonful three times daily.
HOW SUPPLIED: 12-dose bottles containing soluble granules to be reconstituted with 35 cc. of water.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

(Continued on page A-134)



in coronary insufficiency



Metamine® Sustained* helps you dilate the coronaries

METAMINE SUSTAINED (triethanolamine trinitrate biphosphate, 10 mg., in a unique sustained-release tablet) is a potent and exceptionally well tolerated *coronary* vasodilator. Pharmacological studies at McGill University demonstrated that METAMINE "exerts a more prolonged and as good, if not slightly better coronary vasodilator action than nitroglycerin . . . "[1] Work at the Pasteur Institute established that METAMINE exerts considerably less depressor effect than does nitroglycerin.[2] Virtually free from nitrate side effects (nausea, headache, hypotension), METAMINE SUSTAINED protects many patients refractory to other cardiac nitrates,[3] and, given b.i.d., is ideal medication for the patient with coronary insufficiency. Bottles of 50 and 500 tablets. Also: METAMINE, METAMINE WITH BUTABARBITAL, METAMINE WITH BUTABARBITAL SUSTAINED, METAMINE SUSTAINED WITH RESERPINE.

1. Melville, K. I., and Lu, F. C.: Canadian M.A.J., *65*:11, 1951. 2. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap., *83*:367, 1946. 3. Fuller, H. L., and Kassel, L. E.: Antibiotic Med. & Clin. Therapy, *3*:322, 1956.

Thos. Leeming & Co. Inc. New York 17, N. Y.

*Patent applied for

• KENALOG®
(New Product Form)

PURPOSE: Topical corticosteroid.
COMPOSITION: Triamcinolone acetonide.
HOW SUPPLIED: 50 and 150 mg. aerosol spray containers of 3.3 and 10 mg., respectively.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• SELECTRONIC RECORD FILE

DESCRIPTION: Holding up to 200,000 cards, this rotary file provides access to any card in less than three seconds. The file is controlled by a Selectronic keyboard with recessed selector keys. A touch on a key engages a Selectronic "brain," which determines the direction of rotation. Dynamic braking eliminates gliding and coasting. Cards of any size and trays to hold different-sized records may be used. The file measures 84⅝ by 39¾ in. and includes a shelf and storage locker.
PRODUCER: Mosler Safe Company, New York.

• PREDNISOLONE ACETATE AQUEOUS INJECTION

PURPOSE: Adrenocortical steroid therapy.
DOSAGE AND ADMINISTRATION: 0.8 to 1.2 cc. per day, intramuscularly or intraarticularly.
HOW SUPPLIED: 5 cc. vials.
PRODUCER: Philadelphia Ampoule Laboratories, Philadelphia.

• MADRIBON®
(New Package Form)

DESCRIPTION: This long-acting antibacterial is now available in bottles of 100.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, N. J.

• ANALEXIN® AND ANALEXIN-AF®

PURPOSE: Analgesic and muscle relaxant.
COMPOSITION: Each tablet of Analexin contains 200 mg. phenyramidol hydrochloride. Each tablet of Analexin-AF contains 100 mg. phenyramidol and 300 mg. aluminum aspirin.
INDICATIONS FOR USE: Analexin-AF is indicated when pain and musculoskeletal tension are complicated by inflammation or fever, or both.
CAUTION: Mild gastrointestinal irritation, epigastric distress, or pruritus with or without a rash may occasionally occur, but will subside when the dosage is reduced or discontinued.
DOSAGE AND ADMINISTRATION: Analexin: 1 or 2 tablets every four hours; in dysmenorrhea, 2 tablets at onset of pain, followed by 1 tablet every two to four hours as needed; Analexin-AF: 2 tablets every four hours or as required.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Irwin, Neisler & Co., Decatur, Ill.

• SPOROSTACIN® CHLORDANTOIN CREAM

PURPOSE: To treat vaginal moniliasis.
COMPOSITION: Chlordantoin.
DOSAGE AND ADMINISTRATION: One applicatorful applied topically morning and night as indicated.
HOW SUPPLIED: 95 gm. plastic tubes, with or without applicator.
PRODUCER: Ortho Pharmaceutical Corporation, Raritan, N. J.

• ASTRAFER® I.V.

PURPOSE: Treatment of iron-deficiency anemia.
COMPOSITION: High molecular iron carbohydrate complex equivalent to 20 mg. trivalent iron per cubic centimeter.
CAUTION: Contraindicated in pernicious anemia. chronic leukemia, bone-marrow depression and liver damage.
DOSAGE AND ADMINISTRATION: 1.5 cc. initially, increased by daily increments of 1 to 1.5 cc. until a daily level of 5 cc. is reached. Astrafer should be administered intravenously and at a slow rate (not more than 5 cc. in two minutes); the patient should rest for 15 to 30 minutes after each administration.
HOW SUPPLIED: 5 cc. color-break ampules in cartons of 10.
PRODUCER: Astra Pharmaceutical Products, Inc., Worcester, Mass.

Financial Planning
for the Medical Practitioner

A monthly service dealing with the basic problems of increasing your net income and building personal capital . . . *in the face of today's high tax structure*

prepared by the

J. K. LASSER INSTITUTE

for

Postgraduate Medicine

MARCH 1960

Retirement Benefits Under A Tax-Qualified Pension Plan - have much greater value than is realized. A leading bank recently furnished this illustration. An executive, age 45, with salary in the $30-40,000 range is given a $5,000 increase. After taxes, he keeps only about $2,500 of the salary increase. If he successfully invested that after-tax amount each year, he would have a capital sum sufficient to buy an annuity producing $4,000 a year 20 years later at time of retirement. If the salary increase had been invested for him in a tax-favored retirement plan instead, 20 years later it would have compounded to a capital sum sufficient to buy him an annuity producing $10,000 a year for life.

Normally, the self-employed professional man cannot qualify for retirement benefits under a tax-favored retirement plan. Such a plan must be set up by an employer for the benefit of employes. Since the self-employed individual does not qualify as an employe, he can't get added retirement benefits which are possible under an employment retirement plan.

The Doctor Who Practices In Partnership - with other professional men now can secure the added retirement benefits available under a tax-favored employment plan. Tax-protected retirement benefits are available to such individuals if they convert their partnership to an association taxable as a corporation. In two cases, the courts held that a group of doctors became eligible for tax benefits under a qualified retirement plan when that was done. The Internal Revenue Service agrees to the soundness of those decisions. As a partner, a doctor can't qualify for benefits under a tax-sheltered retirement plan but as an employe of his association, he can. How can a partnership be converted to a medical association? For there to be an association, the Service says four corporate tests generally have to be met:

(1) Continuity of life. The association does not end with death, insanity, bankruptcy, retirement, resignation, or expulsion of a member. (2) Centralization of management. One or several members are authorized by all members to make manage-

ment decisions. (3) Limited liability of members such as that which is given stockholders covering debts of their corporation. (4) Transferability of interests. A member can sell or otherwise dispose of his interest without consent of other members.

In Converting Partnership To Medical Association - must all four corporate tests be met if the doctors are to benefit from a retirement plan? The Internal Revenue Service concedes that an association may come into existence even though all four corporate tests are not met fully. It gives these two examples.

Example (1): Seven doctors organize a clinic. Their agreement provides that except on liquidation of the clinic by vote of three fourths of the members, no member has any individual interest in clinic assets; also neither death, insanity, bankruptcy, retirement, resignation, nor expulsion will cause dissolution of clinic. Clinic management is vested in a four-man committee elected by members. While only the committee has power to act for clinic, members of the clinic are personally liable for claims against clinic. Each member has right to transfer his interest to an outside doctor, but he must first give the clinic right to buy his interest at its fair market value.

Example (2): The factual situation is the same as in example (1), but a doctor resigning has power to force clinic liquidation. No member can transfer his interest to another doctor without unanimous consent of all members. While management is vested in a committee, acts of any member (dealing with an outsider without knowledge of committee's power) will bind clinic. Notwithstanding the agreement that each doctor alone is liable for acts of malpractice, all members are personally liable for claims (including malpractice claims) against clinic.

Do both clinics qualify as associations? The Internal Revenue Service says that in the first example only the corporate characteristic of limited liability is missing. The clinic qualifies as an association. There is centralized management, continuity of life, and a modified form of transferability of interests. However, in the second example, the chief corporate characteristics do not exist or are considerably modified. A partnership has been formed - not a medical association. The doctors are not entitled to pension benefits under a tax-qualified retirement plan set up by their clinic for employes.

* * * * *

Tax Protection Of Annuities Is Increased - under another concession by the Internal Revenue Service. The concession adds to the value of an annuity as a method of saving for retirement.

When an annuity approaches maturity, you have a number of elections - all of which now are tax protected.

Election (1): You let the annuity mature for the protection of a steady cash return for your life. On payments in any one year, amounts received up to "annuity exclusion" are exempt from tax. Only payments in excess of the exclusion are taxable income.

Election (2): You find you don't need the protection of a steady cash return for life. You want the cash tied up in the annuity policy for other uses. You surrender the policy. While your profit (excess of cash surrender proceeds over premiums you paid) is ordinary income, you treat such income as if received ratably in current year and two preceding years. So tax on such profit at higher rates is avoided.

Election (3): You find you don't need protection of a steady cash return for life. Nor do you have any current use for cash values in the annuity. You do want to use those cash values as a liquid reserve readily available if needed later. So before maturity of the policy, you elect to receive installment payments of principal and interest, payable over a number of years. But you also reserve the right to demand payment in full at any time. On demand, the insurance company must pay you in full within six months. Normally, the company will pay immediately. The Service now concedes that even though you can convert your policy into cash at any time you are not in constructive receipt of such cash. You have taxable income only as you receive installments or, in case of demand, full payment.

* * * * *

When A Doctor Sells His Home - he can avoid tax on any profit by investing sales proceeds in another residence. That's a relief provision under the tax law which has general application to all taxpayers. Many doctors use part of their homes as an office. If the doctor who practices from his residence sells his home, can he avoid tax on any profit if he reinvests sales proceeds in a new residence?

There is one court decision which inferentially supports deferment of tax on all of the profit in such situation. However, the Internal Revenue Service now has announced its disagreement. If a doctor uses part of his home for an office, he must allocate sales price in part to his home and in part to his office. He can avoid current tax only on that part of sales profit which is attributable to home use. That part of his profit attributable to professional use is subject to current tax.

Teacher's Tax Difficulties May Adversely Affect Doctors - employed by medical institutes, universities, Government agencies,

etc. The teacher was employed by a private educational institution, most of whose students boarded. As a condition of employment, faculty members had to reside at the school. Teachers were furnished board and lodging for themselves and their families without cost to them by the educational institution. Under the tax law, the value of meals and lodgings furnished employes to serve the "convenience of the employer" is not taxable compensation. The Internal Revenue Service agrees to this rule, but is now attempting to limit its application. In the case of the teacher, the Service conceded that he did not have to count his portion of free board and lodging as taxable income. However, it claimed that he did realize income to the extent of food and shelter furnished his family.

The doctor employed by a private organization or Government agency may be required to live on the premises as a convenience to his employer. The value of meals and lodging furnished him personally is not subject to tax. However, value of meals and living quarters furnished his family may be taxed as additional compensation. That value will be taxed if the Service extends its ruling on the teacher to cover the doctor.

* * * * *

A Trip To Canada This Year - might allow you to buy $500 in European imports free of custom duties or import taxes. Canada allows goods to be imported from Europe without duty if shipped sealed to a warehouse for reshipment to another country, e. g., United States. The United States allows you to import up to $200 worth of goods duty free from Canada if you stay there more than 48 hours - up to $500 if you stay over 12 days.

A group of tax-conscious American, Canadian, and British businessmen are setting up "free" shops in Canada, hoping to combine the above rules for bargain sales to Americans buying goods from them. The free shops will be established at entry points in Windsor Hill Island, Niagara Falls and Sarnia. Each free shop will have two buildings. (1) A bonded warehouse open only to store employes and custom inspectors. European goods will be shipped sealed to this warehouse. (2) The other building will be a shop open to American tourists. Samples of warehouse goods will be on display there. You make your selection from samples, pay for goods, and get a sales slip and a customs form in return. Goods will then be mailed from warehouse to your home duty free and under your customs form.

When the "free" shops are established, an American buying through them would be able to purchase goods at a cost which would compare favorably to cost of purchases made by a tourist traveling in Europe.

Now available at cost—$1.50—3-ring loose-leaf binder to hold 24 monthly Lasser reports. Made of blue simulated morocco grain leather; non-soil finish with embossed cushion edge. Send check with name and address to POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

Because he has something you haven't...

People today—because of advances in medicine and the increasing acceptance of the annual physical examination—are living longer.

As a result, industry is making available to workers increased insurance and old-age benefits. Business, for its executives and employees, offers pension plans, profit-sharing, stock options.

What is being done—or *can* be done—for *you?*

Mutual Benefit Life has considered the problem of accrual which you, as an *unincorporated individual,* face.

Whether you are starting in your profession or are already well-advanced in it, a Mutual Benefit Life agent—trained in his calling—can help you plan a long-range or short-range program for True Security now and for whenever you plan to retire.

May we have a Mutual Benefit Life man call on you—when you are least busy? We believe his specialized knowledge can prove helpful and welcome.

you need the protection of TRUE SECURITY—financial planning for you and your family by

MUTUAL BENEFIT LIFE

The Insurance Company for TRUE SECURITY

CLIP AND MAIL TODAY

The Mutual Benefit Life Insurance Company
Agency Dept 4-3
Newark 1, New Jersey

Please send me a free copy of a handbook on the medical profession's financial problems—and their solution, to help me keep more of my earnings. This request does not obligate me in any way.

NAME_____

ADDRESS_____

CITY_____ ZONE____ STATE_____

THE MEDICAL Bookman

► THE YEAR BOOK OF GENERAL SURGERY (1959-1960)

Edited by Michael E. DeBakey, M.D., Professor of Surgery, Baylor University College of Medicine, Houston. 639 pages with 169 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $8.00.

Emphasis on new developments in general surgery and anesthesia is the general feature of the new volume. The section on general surgery is grouped in 23 different subdivisions, essentially by systems. Assuming that the book reflects more activity in some areas of surgery than in others, the shift in emphasis in recent years toward cardiovascular disease is again readily apparent. Another area in which interest is high is the field of homotransplantation of tissue. Although problems of practical application are yet to be solved, a number of successful experimental technics are reported.

Progress in the field of fluids and electrolytes has been considerable. The problems previously associated with intravenously administered fat preparations appear largely solved. Pasteurization of pooled plasma appears to be the answer to the elimination of serum hepatitis transmitted by plasma infusion.

In the field of cancer, the newer aspects reported are investigations in tumor immunity and chemotherapy. For the most part, the numerous reported results of surgical and irradiation treatment of cancer are much the same as in the past several years. Of particular interest are several articles which tend to emphasize that our currently poor results in the surgical management of cancer of the lung can be improved only by earlier operation rather than by radical procedures; in fact, the value of radical pneumonectomy is questioned.

The section on the heart and great vessels reveals the rapid progress being made in these areas. The reports are from widely scattered centers, which reflect the general feverish investigative activity.

Not all the material in the book by any means is limited to investigation and to unusual operations. Reports on management of acute cholecystitis, problems of cystic duct remnants, common duct stones, strictures of the bile ducts, and technical aspects of repair of the bile duct are summarized.

Presented in a digest form, the material gives a panoramic view of current surgical thinking, which indeed is the purpose and most desirable feature of this book. To attempt to read all the original articles, not to mention selecting the desirable ones, would be impractical for the majority of physicians.

Y. S.

► HELP FOR TEN MILLION

By Darrell C. Crain, M.D., Clinical Associate Professor of Medicine, Georgetown University School of Medicine, Washington, D.C. 251 pages, illustrated. 1959, J. B. Lippincott Company, Philadelphia and Montreal. $3.50.

This book is designed for people with arthritis, rheumatism and gout. The fanciful title will serve to lose readers rather than to gain them. If the book is about arthritis, rheumatism and gout, why not say so directly?

The information which this book offers is sound and certainly such as might be needed by a person afflicted with any of these diseases. A useful appendix discusses diets and exercises.

M. F.

(Continued on page A-162)

children won't hide from this ORAL PENICILLIN with INJECTION PERFORMANCE

For both pediatric and adult patients, PEN·VEE K, in either tablet or liquid form, provides high penicillin blood levels rapidly and reliably. It may be prescribed for all infections responsive to oral penicillin . . . and even many usually treated with parenteral penicillin.

The flexibility of dosage form, pleasant taste, and high potency of PEN·VEE K assure acceptability of the full therapeutic dosage.

SUPPLIED: Liquid: raspberry-flavored, 125 mg. (200,000 units) per 5-cc. teaspoonful; peach-flavored, 250 mg. (400,000 units) per 5-cc. teaspoonful. Supplied as vials of powder to make 40 cc. Tablets: 125 mg. (200,000 units) and 250 mg. (400,000 units) in vials of 36.

PEN·VEE® K

Liquid: Penicillin V Potassium for Oral Solution, Wyeth

Tablets: Penicillin V Potassium, Wyeth

Wyeth Laboratories, Philadelphia 1, Pa.

100 ANNIVERSARY 1

Wyeth®

A Century of Service to Medicine

► CANCER OF THE BREAST

Compiled and edited by Willard H. Parsons, M.D., Chief of Staff and Director of Surgery, Vicksburg Hospital, Vicksburg, Mississippi, with 12 contributors. American Lecture Series. 232 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $7.50.

In 10 carefully chosen chapters the editor has compiled the views of well-qualified scientists and clinicians concerning all the important phases of carcinoma of the breast. The authors have been specific in most of their statements and have maintained a conservative attitude in their discussions and opinions. Their wide experience in this field is evidenced in their writings.

The chapter concerning the anatomy of the breast clearly defines the problems discussed in ensuing chapters dealing with the surgical approach to malignant lesions of this organ. A practical and generously illustrated classification of breast tumors is presented, with numerous demonstrations of the necessity for close liaison between surgeon and pathologist at the time the tumor is excised. The relationship between cystic or proliferative lesions of the breast and mammary carcinoma is aptly discussed.

The chapter on "Diagnosis" emphasizes the great importance of early diagnosis and prompt definitive therapy. The author discusses modes of biopsy and urges the unanimous adoption of excisional biopsy.

In the chapter dealing with the surgical approach to cancer of the breast, the authors discuss clearly the advantages and disadvantages of simple, radical and superradical procedures. The reader is impressed by the fact that, after careful individual consideration, the wisest surgical procedure in a single case is determined not so much by the nature of the primary lesion as by the proved or presumed extent of metastasis.

The conservative approach advanced in "The role of the radiologist" is reflected in the view that radiation does not destroy malignant cells. It alters them in such a fashion as to render them more susceptible to the host's natural defense mechanisms or to reduce their aggressiveness. The specific indications for radiation, the dosage, and the role of roentgen therapy as an adjunctive measure are carefully discussed.

The chapter on "Hormonal treatment" deals primarily with the indications for adrenalectomy, pointing out that a significant number of patients with an undeniably hopeless prognosis will derive benefit. Unfortunately, data necessary to compare the results of hypophysectomy with those of adrenalectomy were not available.

In the concluding chapter, it is pointed out that, although the present methods of therapy for malignant mammary lesions are far from ideal, skillful and timely application of available procedures has resulted in a steadily increasing percentage of five year survivals.

This book is a practical volume for anyone dealing with cancer of the breast.

H. K. I.

► PATIENT CARE AND SPECIAL PROCEDURES IN X-RAY TECHNOLOGY

By Carlo Hocking Venners, R.N., formerly Surgical Supervisor and Clinical Instructor, and John C. Watson, R.T., Director of Courses in X-ray Technology, University of Minnesota Hospitals, Minneapolis. 203 pages with 61 illustrations. 1959, The C. V. Mosby Company, St. Louis. $5.75.

Everyone working with roentgenographic technics is directly or indirectly concerned with the proper handling of patients. Although this is an obvious statement, virtually no attention has been given to it in the basic texts used in training x-ray technicians. The authors of this well-written, compact book have performed a great service in rectifying this deficiency.

The role of the technician in relation to medicine, the hospital and patient care is outlined. The text even includes patient-technician relationships. In addition, the technician is briefed in technics for handling both conscious and unconscious patients. First-aid procedures pertaining to roentgenographic emergencies are given.

Many roentgenographic technics are discussed from the viewpoint of their purposes rather than in terms of the physical factors involved. Nursing problems are considered and sterile technic in special and routine procedures is explained.

Other subjects which are well covered include adapting bedside roentgenography to the needs of various patients, the technician's duties in an x-ray department, and the role of roentgenography in operating and recovery rooms.

S. B. F.

(Continued on page A-164)

FOUND: a dependable solution to
"the commonest gynecologic office problem"
"VULVOVAGINITIS, CAUSED BY TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, Haemophilus vaginalis, or other bacteria, is still the commonest gynecologic office problem . . . cases of chronic or mixed infection are often extremely difficult to cure." Among 75 patients with vulvovaginitis caused by one or more of these pathogens, TRICOFURON IMPROVED cleared symptoms in 70; virtually all were severe, chronic infections which had persisted despite previous therapy with other agents. "Permanent cure by both laboratory and clinical criteria was achieved in 56. . . . "
Am. J. Obst. 77:155, 1959
TRICOFURON®
Improved
■ Swiftly relieves itching, burning, malodor and leukorrhea ■ Destroys Trichomonas vaginalis, Candida (Monilia) albicans, Haemophilus vaginalis ■ Achieves clinical and cultural cures where others fail ■ Nonirritating and esthetically pleasing
2 steps to lasting relief:
1. POWDER for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.
2. SUPPOSITORIES for continued home use each morning and night the first week and each night thereafter—especially during the important menstrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.
Rx new box of 24 suppositories with applicator for more practical and economical therapy.
NITROFURANS—a unique class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

► SYNOPSIS OF EAR, NOSE AND THROAT DISEASES

By Robert E. Ryan, M.D., Department of Otolaryngology, St. Louis University School of Medicine, St. Louis, William C. Thornell, M.D., Assistant Professor, Department of Otolaryngology, University of Cincinnati College of Medicine, Cincinnati, and Hans von Leden, M.D., Assistant Professor of Otolaryngology, Northwestern University Medical School, Chicago. 383 pages with 59 illustrations. 1959, The C. V. Mosby Company, St. Louis. $6.75.

In the preface to this pocket-sized book, the authors state that it "was written to serve as a handy guide for the busy family physician, the intern, and the medical student and as a ready reference for nurses and speech or voice pathologists." Obviously, in a treatise of this size only very superficial coverage can be given to any subject. The primary intent of the authors was probably to help the "busy family physician" more than to help the intern or nurse.

I have had a great deal of experience in finding out what information the general practitioner needs and wants on diseases of the ear, nose and throat. He needs up-to-date information on progress, diagnosis and the proper therapy to administer. Much of this is missing in the section devoted to the ear. For instance, the family doctor is interested in having some general ideas on the meaning of air-conduction audiograms which are brought to him by the parents of the school children who are his patients. Therefore, an illustration and discussion of an audiogram could well have a place in this book. In recent years, advances have been made in the surgery for conduction hearing loss in otosclerosis and in the repair of eardrums and middle ears damaged by chronic disease. These common conditions are merely mentioned in this book, while the complications of otitis media, now relatively rare, are discussed in more detail than seems necessary. In addition, many patients, especially the elderly, ask general questions of the family physician about the use of hearing aids; however, I could find no information on this subject.

The coverage on the nose and throat seems adequate for a work of this size, but the book would have been more helpful to the busy family physician if more specific information on therapy had been included.

L. R. B.

► CARE OF THE PATIENT WITH A STROKE

By Genevieve Waples Smith, R.N. 148 pages, illustrated. 1959, Springer Publishing Company, Inc., New York. $2.75.

When Mrs. Smith, who is a nurse, was compelled to care for her husband when he had a stroke, she found that the home nursing of such a patient raises many problems which she had to solve for herself. Some help was obtained from a rehabilitation center. Out of her experience and with the aid of the physicians, dietitians and nurses who helped her, she evolved an outline which should be of immense help to anyone who is faced with a similar problem.

One might wish that Mrs. Smith had written somewhat more personally, since she constantly refers to her husband as "the patient." Except for such minor criticism, this is a book that is exceedingly practical and helpful and quite certainly worth all that anyone who needs it might invest in it.

M. F.

► THE ACUTE MEDICAL SYNDROMES AND EMERGENCIES

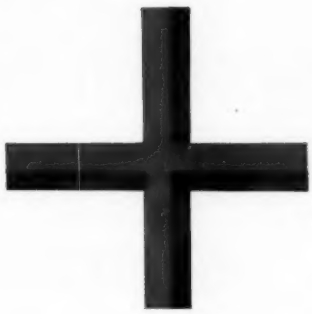
By Albert Salisbury Hyman, M.D., Associate Clinical Professor of Medicine, New York Medical College, New York, with five collaborators. 442 pages. 1959, Landsberger Medical Books, Inc., New York. $8.75.

The particular topics discussed in this text are not the selections of the author and his collaborators; they are the result of a nationwide poll in which physicians in active practice were asked to list the types of important acute medical problems they had been called on to treat in the previous five years. A discussion of these emergencies makes up the content of the book.

Six types of acute medical syndromes are discussed, including cardiovascular, gastrointestinal and diabetic emergencies, renal crises, and barbiturate intoxication. The practical experience of the authors and much data from other sources form the basis for these discussions. The book is concise and well written, and the authors accomplish their purpose very well.

I. P. F.

(Continued on page A-168)



for

+ ***positive anabolic gains***
+ ***marked sense of well-being***
+ ***direct control of your patient***
+ ***greater economy***

One injection of DURABOLIN each week often induces a marked sense of well-being in the asthenic, undernourished, or "run-down" patient. Outlook and appetite improve. Sustained, positive nitrogen balance is established. Solid muscular tissue develops. Weight is gained without edema. The safest and most potent tissue-building agent, DURABOLIN is also the easiest to use and most economical. The physician injects it each week. There can be no unfilled prescription, no forgotten dose. Progress is observed directly. Adults: 25 mg. (1 cc.) i.m. weekly, or 50 mg. (2 cc.) every second week. Children: half adult dosage. ORGANON INC., Orange, N. J.

olin®

Nandrolone phenpropionate injection, ORGANON

Organon

► CLINICAL AUSCULTATION OF THE HEART

By Samuel A. Levine, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, Boston, and W. Proctor Harvey, M.D., Associate Professor of Medicine, Georgetown University School of Medicine, Washington, D.C. Ed. 2. 657 pages with 660 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $11.00.

In the past decade advances in cardiac surgery, cardiac catheterization and phonocardiographic technics have caused a tremendous resurgence of interest in auscultatory phenomena. The second edition of this text covers the entire range of congenital and acquired heart disease most exhaustively, being adequately documented with phonocardiographic strips. The sound records are generally of excellent quality and adequately labeled. The introduction carefully details the technics of adequate auscultation, the proper equipment necessary, and the importance of devoting adequate time and concentration to the assessment of physical findings. It properly indicates the deficiencies in modern-day teaching of cardiac auscultation.

Only a few statements, observations or omissions appear worthy of mention. In the discussion of mitral insufficiency, no mention is made of the early, short diastolic murmur often associated with a thrill that may be present in patients who have pure, severe mitral insufficiency. No reference is made to the patient with rupture of the chordae tendineae of the posterior mitral leaflet whose murmur is referred particularly to the aortic valve area and the carotid vessels because the regurgitant jet is directed this way; such a patient commonly is thought to have disease of the aortic valve in addition to mitral insufficiency because of the transmission of the murmur. The discussion of atrial septal defect states that cardiac catheterization is done primarily to assess the presence and severity of pulmonary hypertension; while the procedure is necessary in some patients for this reason, the main purpose of catheterization in such defects is to exclude associated partial anomalous pulmonary venous connections. In the section devoted to atrioventricular canal defects, it is stated that left axis deviation may be present on the electrocardiogram; a more accurate statement would be that it is almost invariably present.

This new edition can be highly recommended to all physicians and medical students interested in increasing their competency with the stethoscope and their understanding of cardiac hemodynamics.

R. O. B.

► ATLAS OF ROENTGENOGRAPHIC POSITIONS

By Vinita Merrill, formerly Educational Director, Picker X-Ray Corporation, White Plains, New York. Ed. 2. Vols. 1 and 2. 664 pages, illustrated. 1959, The C. V. Mosby Company, St. Louis. $32.50.

The first edition of this work, published in 1949, is recognized as a standard text in its field. The aim of the second edition, according to the author, is the assembly of material: a compilation of positions and the inclusion of an extensive bibliography. The author has accomplished this aim.

While this edition is a continuation of the first, new technics have been added. With only a few minor exceptions, for example, the discussion on angiography, the material is up to date.

Many features make this volume an ideal text and reference for the technician. It contains accurate and adequate anatomic material and a comprehensive glossary of anatomic and medical terms. Throughout the book correct terms are used. The misnomer "dye" is deleted in favor of the term for the correct contrast medium. There are numerous illustrations, consisting of photographs and line drawings of the correct roentgenographic positions and of the resulting views. Multiple methods of obtaining a given view are included, and contraindications to a given position, such as suspected fractures, are clearly indicated. The index lists positions anatomically and by eponyms.

The physician who has his own x-ray equipment and desires to increase its value as a diagnostic tool will find this atlas a great aid. To the technician and radiologist engaged in teaching, this work is invaluable not only as a text but also as a source of an extensive bibliography.

N. M. S.

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Listings of books received are on pages 305 and 415.

predictable weight loss

FOR THE VICTIM OF OVEREATING AND "UNDERDOING"...

Rx

BIPHETAMINE®

A 'STRASIONIC' RELEASE ANORETIC RESIN

Employing 'Strasionic' release, Biphetamine's appetite appeasing, mildly invigorating action is uniformly prolonged for 10 to 14 hours with a single capsule dose. Caloric intake is reduced, energy output is increased. Weight loss is predictable—a comfortable 1-3 lbs. a week in 9 out of 10 cases.

"STRASIONIC RELEASE" MAKES THE BIG DIFFERENCE

BIPHETAMINE® '20' Resin
Each black capsule contains:
d-amphetamine ..... 10 mg.
dl-amphetamine ..... 10 mg.
as resin complexes

BIPHETAMINE® '12½' Resin
Each black and white capsule contains:
d-amphetamine .....6.25 mg.
dl-amphetamine .....6.25 mg.
as resin complexes

BIPHETAMINE® '7½' Resin
Each white capsule contains:
d-amphetamine .....3.75 mg.
dl-amphetamine .....3.75 mg.
as resin complexes

Single Capsule Daily Dose 10 to 14 hours before retiring

℞ Only. Caution: Federal law prohibits dispensing without prescription.

Biphetamine—made and marketed ONLY by **STRASENBURGH LABORATORIES** ROCHESTER, N.Y., U.S.A.

Originators of 'Strasionic' (sustained ionic) Release

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Jan. 1—This day recovering from yesterday and last night. Reading now on Christian Science healing, and then read again "The Most of S. J. Perelman," a marvelous antidote.

Jan. 2—At my editing, and in the afternoon to the Standard Club, where Judge Brown and Gladys received for Howard and Miss Kassel. Here chatted with Judges Igoe and Kerner, the young Bettmans, and Sid Cohn from Fond du Lac.

Jan. 4—Reading now "In the Days of McKinley," by Margaret Leech, a biography which tells of life in Canton, Ohio, and Washington in the 1890s and of the trials of an ambitious man with an epileptic wife.

Jan. 5—To lecture on quackery at Northwestern University Medical School, where Richard Young introduced me, and there were present Van Dellen, Fred Stenn, Barry Anson and a fine, attentive lot of students. Gil Cooper came to luncheon and we talked some hours on editing.

Jan. 6—Came Dick Lundy looking much like John must have looked at his age. To the Standard Club for lunch with Feiwell and Stanley J. Kann and Harry Epstine of the board of Montefiore Hospital in Pittsburgh. In the evening to the Union League for cocktails and spoke to the Boswell Club, being made a doctor of frustration and wordly wisdom, with the title "Sam'l Pepys." Here Phil Davis presided and Ted Remer introduced. Here were Robert McCormick, Faherty, Willis Potts, Mendelsohn, Judge Lyle and many more for a fine dinner.

Jan. 7—The latest edition of A. Sachar's "History of the Jews" at hand with a special statement of the relationship between communism and anti-Semitism. In the evening to hear Markevitsch conduct the symphony orchestra for a wildly enthusiastic audience, especially excited over some selections played here for the first time, particularly a tricky work exemplifying the qualities of each instrument. This, by Benjamin Britten, is "The Young Person's Guide to the Orchestra."

Jan. 8—First came Ed Stegen for a conference on the Brain Research Foundation, and then met with Clayton, Bluedorn, Leland Case and Bernstein to plan a new development of *The Quill.* In the evening watched Art Carney and Celeste Holm on television.

Jan. 9—At the Shoreland where were all the deans discussing their financial problems. So had luncheon with Houston Merritt and Sevringhaus, meeting also Caughey, Harrell, Deitrick, Coggeshall, Truslow and many more. This afternoon came Sam Mantel to discuss a problem of the aged in our own family.

Jan. 10—At my desk and to the Jackson Park Hospital to see the improvements. Betweentimes came Remer and Edelman to discuss the removal of the congenital heart disease study from the Hektoen Institute to the Children's Memorial Hospital.

Jan. 11—To see Harry Asher, who maintains my dental equipment. Then to Sarah Siddons' Walk in the Ambassador and sat with Forrest Tucker of "The Music Man" and Patty Clark of the Chez Paree and helped install the new president of the Variety Club Auxiliary. After some hours at the desk to the Congress to speak at the inauguration of Bill Margolis as president of the Variety Club. Here sat with Jack Brickhouse, who spoke also.

Jan. 12—Busy with the writing of many items, in particular the periodicals. At night to dine sumptuously at La Fitte in the Churchill with the Larry Joselits, played gin profitably with Krieger and Berkson, and exchanged new stories with Sylvia Marks.

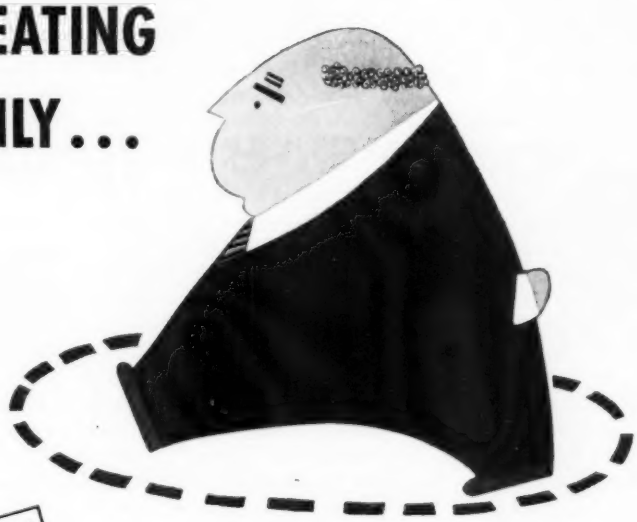
Jan. 13—By the noon plane to St. Louis, and at the Coronado Hotel met Monsignor McGowan, Charles Berry, Father Flanagan and Anthony Rourke. To a great dinner where came the sisters who administer the Catholic hospitals. Here old Pepys gave the tenth annual Schwitalla Lecture. The subject was "The Hospital's Fight for Survival." Father Schwitalla, now 78, responded.

Jan. 14—By the plane to New York and directly from Idlewild to Morris Plains to meet with Bill Lasdon, Len Scheele, Elmer Bobst, Arnow, Clark and Whitney. Then to Herbert Mayes' to dine and play at bridge with Herbert, Charles Goren and Richard Frey, and in the first two rubbers the team of Mayes and Pepys simply overwhelmed the experts.

(Continued on page A-196)

predictable weight loss

FOR THE VICTIM OF OVEREATING ONLY...



Rx NEW

IONAMIN™

A 'STRASIONIC' ANORETIC — PHENYL–*TERT.*–BUTYLAMINE RESIN

Employing 'Strasionic' release, Ionamin's appetite appeasing action is uniformly prolonged for 10 to 14 hours with a single capsule dose. Caloric intake is reduced to a level consistent with the energy output of an "active" overeater. Weight loss is predictable—a comfortable .221 pounds per day in average cases.

"STRASIONIC RELEASE" MAKES THE BIG DIFFERENCE

Rx Only.
Caution: Federal law prohibits dispensing without prescription.

IONAMIN™ '30'
Each yellow capsule contains:
phenyl-tert.-butylamine .. 30 mg.
as a resin complex

IONAMIN™ '15'
Each grey and yellow capsule contains:
phenyl-tert.-butylamine .. 15 mg.
as a resin complex

Single Capsule Daily Dose 10 to 14 hours before retiring

Ionamin—made and marketed ONLY by STRASENBURGH LABORATORIES
ROCHESTER, N.Y., U.S.A.

Originators of 'Strasionic' (sustained ionic) Release

Jan. 15—For breakfast came Bill White and thereafter Max Geffen and Bill Lasdon, and we conferred until afternoon. Then came Peter Warren and Ted Gotthelf to work on "The Voice of Medicine." Thereafter came Mark Soroko and then the Friedells and Milton Runyon.

Jan. 16—To Taylor-Carlisle's to see the new books. Then chatted with Terese Rivers, and after lunch to see an ethnologic film called "The Mating Urge," which deals obliquely with the courting habits of the aborigines. Next, to see Andy Griffith in a wholly delightful musical called "Destry Rides Again."

Jan. 17—Reading now an amazing book about Sicily called "The Ten Pains of Death," by Gavin Maxwell. In the afternoon to visit the new Guggenheim Museum built by Frank Lloyd Wright. Found the building amazingly beautiful and utilitarian, but the modernistic pictures and sculptures were well beyond my comprehension.

Jan. 18—Early came Ted Gotthelf and Peter Warren, then Drs. Phil Thorek, Joe Kirsner, Lester Dragstedt and Asher Winkelstein. So we made a run-through of a panel on peptic ulcer and then to the Anra studio for the recording. In the afternoon for a press conference with Marguerite Clark, Barbara Younker, the Netherlands consul, and many more. To dine in the Empire Room with the Gotthelfs and then to see Rex Harrison in "The Fighting Cock."

Jan. 19—For breakfast came Mel Glasser to talk of the work of the National Foundation, then Bill Marsden on *World-Wide Abstracts*. At noon to Brentano's and Doubleday's. In the afternoon came Algernon Reese to talk of the book on tumors of the eye, and for cocktails Elmer Bobst and Al Driscoll with reports of new activities. Then with Bill and Mildred Lasdon to "21," where warmly greeted by all the "maîtres" and chatted with Basil and Hazel O'Connor, who were off to see the Collingwood trailer for the March of Dimes.

Jan. 20—To breakfast with Paul Robinson of Johnson & Johnson and then for a conference with Paul Warwick. Here were Welsh, Baldwin and the staff. Next to confer and lunch with Mel Glasser and after that to see Peter Warren. Much excitement about Anita Bloch's "Necessary End," a good novel about the drug industry. In the evening to Asher Winkelsteins' to dine amidst his treasures of art, meeting here my old friend Arthur Fishberg, a leader in hypertension, and Goldfarb, who gave a million to Brandeis University for its library. Then to see a brilliant cast do Shaw's "Heartbreak House."

Jan. 21—By plane to Baltimore and to visit the Lutheran Hospital, which has a kitchen built in 1823. Thereafter, to make tapes for two television news shows. In the evening to speak to some 1200 persons at the Fifth Regiment Armory on behalf of a new structure to replace the main building built in 1870. At dinner sat next to Albert Warfield, whom I found a delightful conversationalist, and Carl Hauswald, who is president of the hospital's board.

Jan. 22—To Atlantic City by plane, and greeted at the Traymore by Bill Stern. The weather being glorious, walked the Boardwalk, observing the rebuilding of the walk and of the convention hall. Reading now a British novel called "Billy Liar," which British critics have hailed as funny and which to American taste is hardly humorous.

Jan. 23—Lay late and edited the book on the heart. Then in beautiful sunshine walked the length of the Boardwalk and dined at Hackney's.

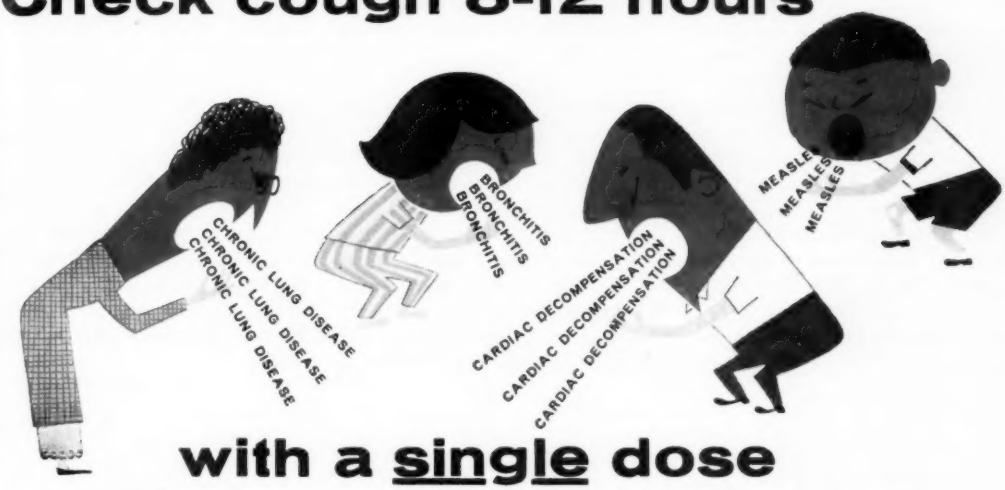
Jan. 24—Again resting late; again walking in the sun, and spent some hours on the *New York Times*. In the afternoon by plane to Washington, meeting Haney and some Korean friends.

Jan. 25—To Fayetteville in North Carolina and to see the great 200 bed hospital in Lumberton which was built just a few years ago and already needs an addition. Here, with George Harris and James Felts of the Duke Endowment, J. M. DeVane, administrator, and Dr. T. H. Mees, viewed all the institution. In the library found the late issues of POSTGRADUATE MEDICINE showing signs of most usage. In the evening to speak in the school to some 500 persons, and meeting Drs. Allen, Hedgepath and many more and also Professor Gale, president of Pembroke Academy.

Jan. 26—After a fine night in the Betsy Ross Motel at Fayetteville, by plane to Charlotte and Chicago. And now news of the sudden death of Max Thorek, a great and colorful personality. At home, as usual, innumerable messages and documents were awaiting attention, and they are always exciting after a journey. En route read a scholarly treatise, "Sex Variant Women in Literature," by Jeannette H. Foster.

(Continued on page A-198)

Check cough 8-12 hours



with a single dose

Rx TUSSIONEX®

A 'Strasionic' Antitussive • Dihydrocodeinone Resin—Phenyltoloxamine Resin

"STRASIONIC RELEASE" MAKES THE BIG DIFFERENCE

- Permits Natural Discharge of Mucus
- Predictable Antitussive Action
- Minimum Amount of Narcotic

TWO FORMS: Tussionex Thixaire™ Suspension • Tussionex Tablets

Each teaspoonful (5c.c.) or tablet provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes.

Dose: 1 teaspoonful or tablet q 12 h. Children under 1 year, ¼ teaspoonful q 12 h; 1-5 years, ½ teaspoonful q 12 h.

Rx only. Class E .axable narcotic.

Tussionex—made and marketed only by

STRASENBURGH LABORATORIES
ROCHESTER, N.Y., U.S.A.

Originators of 'Strasionic' (sustained ionic) Release

Jan. 27—At noon to see Gene Stein for a photograph. Then to the kickoff luncheon for the Chicago Heart Association, where Emory Foote presided and Bill Veeck spoke. Art Snider conducted a panel with Katz, Oglesby Paul and old Pepys, and Katz said all the things we call "sin" cause hardening of the arteries. So old Pepys suggested a grant for the study of sin. Next to the funeral services for Max Thorek in a chapel packed to the doors with notables from far and near. To tea came Robert Portis of Los Angeles. Next to the Merchants' Club, where Dr. Fred and Olive Bruner were hailed by hundreds on her retirement from Spalding School. The evening ended with a great dinner of the Solomon Foundation at the Ambassador Hotel. Here Irv Kupcinet was inaugurated as president. Karl Meyer and old Pepys spoke, and Allen King entertained delightfully with tales of travels and the children.

Jan. 28—To participate with amusing conversations on Don McNeill's Breakfast Club. The Northern girl said, "Men are all alike," and her Southern friend said, "Men are all ah like too." Then all the day at the desk, and read "The Golden Scalpel," by Seymour Kern, a novel of medical practice in Los Angeles in the lower levels—not much good but interesting.

Jan. 29—Spent some hours with Roy Gibbons of the *Tribune* discussing problems of the aged. In the afternoon an interview on "The Voice of Medicine." In the evening came Justin and Ann with the progeny, who are lots of fun and excitement. Danny asked me for a copy of "Germany in the Center of the Earth," thus modernizing Jules Verne.

Jan. 30—To visit Barbara picking up Rosemary, and in the afternoon watching all-star golf. At night with the Friedells and Kirsners to hear the Moscow Symphony, during which Gilels startled the audience with his virtuosity at the piano.

Jan. 31—With the children visiting the cat show; the cat is not an understandable animal. To the new Foundlings Home, seeing Karl Meyer, the chief; Fred Hertwig; Sam Hoffman; and about two thousand others. Next to call on Fanny Thorek and Philip and to remember the great Max. Thereafter to Riccardo's, where Harold Aronson showed his paintings to a hundred friends. While there, traded anecdotes with Billy Goodman and Goldenson. At home, news of the death of my great friend S. DeWitt Clough, philanthropist and leader.

The Medical Muse

RICHARD ARMOUR

NOT-SO-GOOD OLD DAYS

Think how it must have been before
The days of anesthesia,
When doctors couldn't say, "Take this,
I'm sure that it will esia."

Think how a patient screamed and yelled
And even ran through town
Unless, while he was being sliced,
Two others held him down.

What pain there must have been, back then!
How patients feared the knife!
(But while you're sympathizing, think
About the doctor's life.)

TABOO OR NOT TABOO

The prostate gland is strangely, and unnecessarily, taboo in conversation.—*News item.*

Just listen to the ceaseless yak
Of him, the poor insomniac,
Or hear for hours, and show no doubt,
The chap who had a kidney out.

How tirelessly a man will speak
Of how he had a narrow squeak
From gallstones or from hypertension.
But prostate trouble? Not a mention.

If doctors only could convince
Their patients that they needn't wince
At whispers of the prostate gland,
Well, conversation would be grand!